CELL INJURY AND ADAPTATIONS
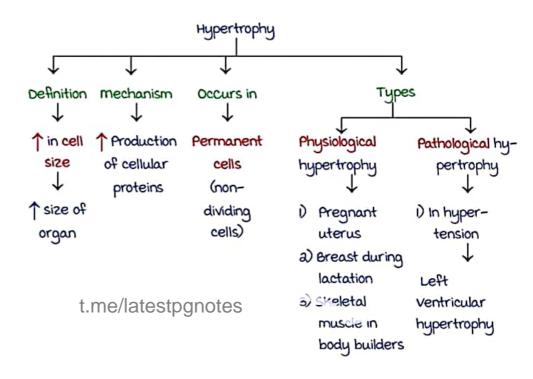
Causes of cell injury
00:01:23

1) Hypoxia – m.c Cause of cell injury

```
                          |
        ┌─────────────────┼──────────────────┐
        ↓                 ↓                  ↓
     m.C.C. of       Cell most sensitive   Cells least sensitive
     hypoxia           to hypoxia            to hypoxia
        ↓                 ↓                  ↓
     Ischemia           neurons       Fibroblasts > Skeletal muscles
```

a) Ischemia
3) Physical agents
4) Chemical agents
5) Infectious agents
6) Genetic diseases
7) Immunological diseases

t.me/latestpgnotes
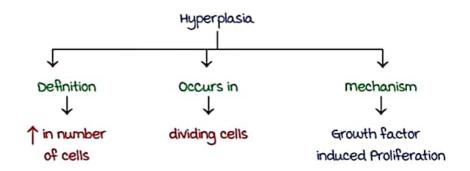
Depending on Nature & Severity
of cell injury

```
        ┌────────┬──────────┬──────────┬──────────┬──────────┐
        ↓        ↓          ↓          ↓          ↓
   Adaptation Reversible cell Irreversible  Pathologic   intracellular
        ↓        injury     cell injury  calcifications  accumulation
 · Hypertrophy    ↓            ↓
 · Hyperplasia · If injurious  Cell death
 · metaplasia    stimuli is      ↓
 · Atrophy       removed    ┌────┬──────┬──────────┬──────────┐
                  ↓         ↓    ↓      ↓          ↓
              Cell returns  Apoptosis Necrosis Necroptosis Pyroptosis
                 to its
              normal state
```

Active space

The organelles affected in cell injury

Nucleus   mitochondria   Plasma membrane   Rough Endoplasmic
Reticulum (RER)

Cellular adaptations - hypertrophy   00:10:43

Hypertrophy

Definition   mechanism   Occurs in   Types

↑ in cell   ↑ Production   Permanent   Physiological   Pathological hy-
size   of cellular   cells   hypertrophy   pertrophy
             proteins   (non-
↑ size of   dividing   1) Pregnant   1) In hyper-
organ   cells)   uterus   tension
                                           2) Breast during
                                              lactation   Left
                                           2) Skeletal   ventricular
                                              muscle in   hypertrophy
                                              body builders

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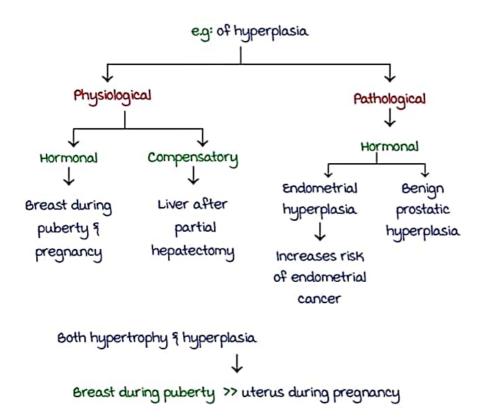
Cellular adaptations – hyperplasia   00:14:33

Hyperplasia

Definition   Occurs in   mechanism

↑ in number   dividing cells   Growth factor
of cells   induced Proliferation

e.g: of hyperplasia

├── **Physiological**
│   ├── **Hormonal**
│   │   └── Breast during puberty & pregnancy
│   └── **Compensatory**
│   └── Liver after partial hepatectomy
└── **Pathological**
    └── **Hormonal**
        ├── Endometrial hyperplasia
        │   └── Increases risk of endometrial cancer
        └── Benign prostatic hyperplasia

Both hypertrophy & hyperplasia
↓
Breast during puberty >> uterus during pregnancy

Cell adaptations – metaplasia 00:19:10

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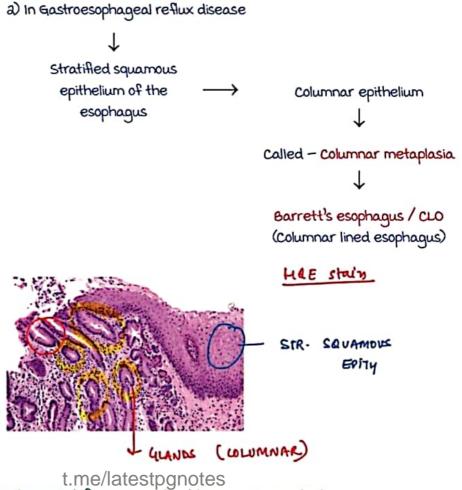
metaplasia
├── **Definition**
│   • Reversible change of one differentiated cell type into another cell type
└── **mechanism**
    • Reprogramming of stem cells
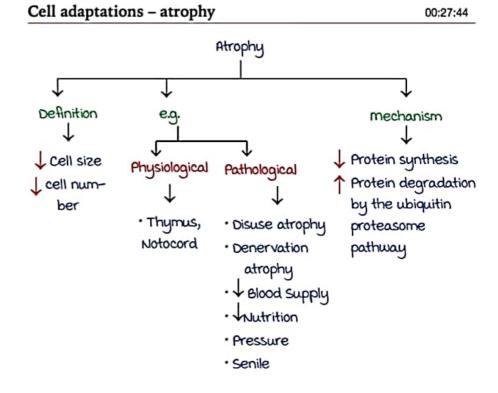
• e.g: m.c. – 1) Respiratory epithelium in smokers
↓
• Pseudostratified ciliated columnar epithelium ⟶ **Stratified squamous epithelium**

called – Squamous metaplasia

Active space

a) In Gastroesophageal reflux disease

↓

Stratified squamous
epithelium of the   ⟶   Columnar epithelium
esophagus

↓

Called – Columnar metaplasia

↓

Barrett's esophagus / CLO
(Columnar lined esophagus)

H&E stain

STR· SQUAMOUS
EPITY

↓ GLANDS (COLUMNAR)

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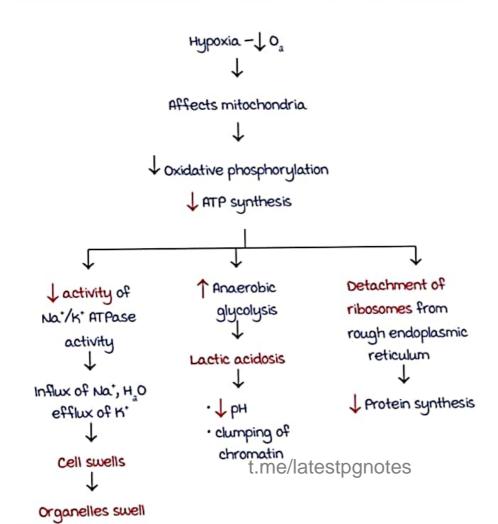
• Vitamin A deficiency can lead to squamous metaplasia

• Connective metaplasia – e.g. myositis ossificans

Cell adaptations – atrophy   00:27:44

Atrophy

```
              Definition          e.g.                        mechanism
                 ↓                                                ↓
             ↓ Cell size    Physiological  Pathological    ↓ Protein synthesis
             ↓ cell num-          ↓             ↓          ↑ Protein degradation
                ber         • Thymus,    • Disuse atrophy     by the ubiquitin
                             Notocord    • Denervation        proteasome
                                           atrophy            pathway
                                         • ↓ Blood Supply
                                         • ↓ Nutrition
                                         • Pressure
                                         • Senile
```

Active space

Reversible cell injury

00:30:22

Hypoxia — $\downarrow O_2$

$\downarrow$

Affects mitochondria

$\downarrow$

$\downarrow$ Oxidative phosphorylation

$\downarrow$ ATP synthesis

$\downarrow$ activity of Na⁺/K⁺ ATPase activity

$\downarrow$

Influx of Na⁺, H₂O efflux of K⁺

$\downarrow$

Cell swells

$\downarrow$

Organelles swell
- Endoplasmic reticulum
- mitochondrium
- membrane blebs
- myelin figures (water deposits in membrane layers)

$\uparrow$ Anaerobic glycolysis

$\downarrow$

Lactic acidosis

$\downarrow$

- $\downarrow$ pH
- clumping of chromatin

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Detachment of ribosomes from rough endoplasmic reticulum

$\downarrow$

$\downarrow$ Protein synthesis

- m.c organelle affected in reversible injury

$\downarrow$

mitochondria

- m.c morphological feature — cellular swelling / hydropic change

Active space

Irreversible cell injury

00:38:19

• Characteristic change — Profound disturbances in cell membrane

severe mitochondrial damage

Release of lysosomal enzymes
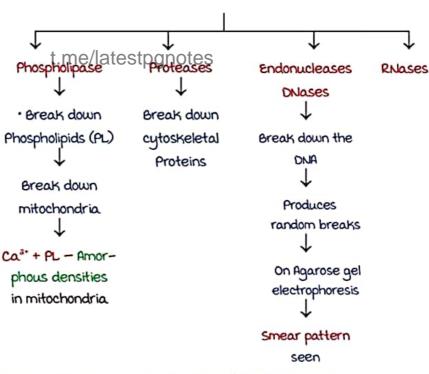
• Due to profound disturbances in cell membrane

↓

Cell will lose its selective permeability

↓

Completely permeable

↓

↑ Cytosolic Ca^{2+}

↓

Activation of enzymes

Phospholipase	Proteases	Endonucleases DNases	RNases
↓	↓	↓	
• Break down Phospholipids (PL)	Break down cytoskeletal Proteins	Break down the DNA	
↓		↓	
Break down mitochondria		Produces random breaks	
↓		↓	
Ca^{2+} + PL — Amorphous densities in mitochondria		On Agarose gel electrophoresis	
		↓	
		Smear pattern seen	

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• Clinical correlation — In myocardial infarction, hepatitis

↓

enzymes measured in plasma

↓

because cell is completely permeable
and contents leak out into plasma

Active space

Irreversible cell injury – nuclear changes

00:44:17

Pyknosis ⊙
(Clumping of nucleus chromatin)
↓

Karyorrhexis ⊛
(Fragmentation of nucleus)
↓

Karyolysis ○
(Dissolution of nucleus)

• m.c – morphological feature of irreversible cell injury
↓

Flocculent amorphous densities in mitochondria
↓

Can only be seen on electron microscopy

• most important light microscopy feature of irreversible cell injury
↓

Nuclear changes

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Active space

CELL DEATH

Necrosis

By 2 Processes

→ Denaturation of proteins

→ Enzymatic digestion of cells

Types : → Coagulative

→ Liquefactive

→ Fat

→ Caseous

→ Fibrinoid

→ Gangrenous

Coagulative Necrosis
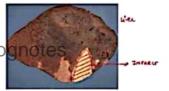
- mC type of Necrosis
- Occurs in all solid organs, except brain
- Example: liver, Kidney, heart, spleen
- mC organ affected : Heart
- mechanism: Denaturation of proteins
- Causes: → Hypoxia
  → Severe Burns
  → Zenker's Degeneration : Coagaulative Necrosis occuring in patients with severe toxemia like typhoid

  ↓

  Affects muscles like rectus abdominis and diaphragm

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- H & E : 1. Cell architecture /outline is preserved
  2. Cells become eosinophilic
  3. cells have glossy appearance

  ↓

  loss of glycogen
  4. cells have a moth eaten appearance (due to loss of organelles)

Active space
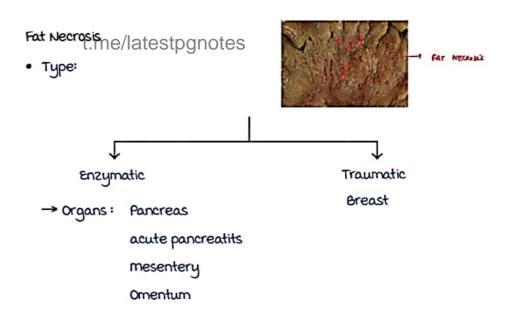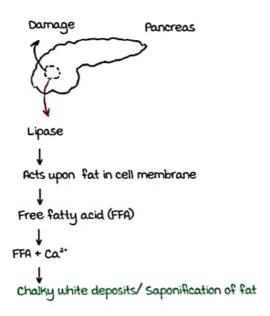
Liquefactive Necrosis /Colliquative Necrosis

- Occurs in: Brain

        Fungal /Bacterial inflection

        Abscesses

- Enzymatic digestion of cells
- Cell outline is not preserved
- Wet gangrene

Caseous Necrosis

- Cottage cheese like appearance
- Histology : Pink, granular appearance
- Example   I. TB (mycolic acid → ↑lipid content)

        2. Fungal infection like : Histoplasmosis

                Coccidioidomycosis

- Can be considered to be a type of coagulative necrosis.
- Can be considered to be coagulative + liquefactive necrosis

Fat Necrosis

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- Type:

```
                    |
        ┌───────────┴───────────┐
        ↓                       ↓
    Enzymatic                Traumatic
                             Breast
  → Organs :  Pancreas
              acute pancreatits
              mesentery
              Omentum
```

Active space

Damage   Pancreas

↓
Lipase
↓
Acts upon fat in cell membrane
↓
Free fatty acid (FFA)
↓
FFA + Ca²⁺
↓
Chalky white deposits/ Saponification of fat

Necrosis : Fibrinoid   00:14:06
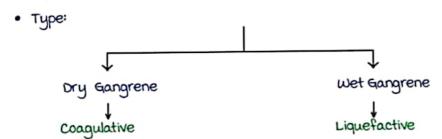
Fibrinoid Necrosis

- In vessels

- In type 2 or 3 Hypersensitivity reaction due to deposition of immune complex

- material : Pink, Fibrin like

- Example: 1 Aschoff Nodules
            2 PAN Vasculitis
            3 malignant hypertension

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Gangrenous Necrosis

- Type:

Dry Gangrene   Wet Gangrene
↓   ↓
Coagulative   Liquefactive

Apoptosis   00:19:39

- Genetically programmed cell death
- Active process

Active space

• Single or small groups of cells

Example: Physiological

I.   Embryogenesis
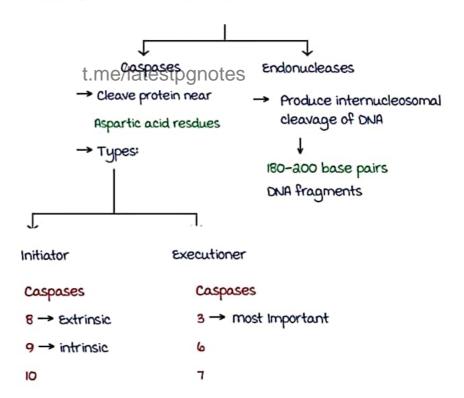
2.   Involution of hormone dependant tissues upon hormone withdrawal

3.   Endometrial shedding during menstrual cycle

4.   Death of harmful self reactive lymphocytes

Pathological

I.   DNA damage

2.   Accumulation of misfolded protein

3.   Cell death in infections like hepatitis

mechanism of Apoptosis
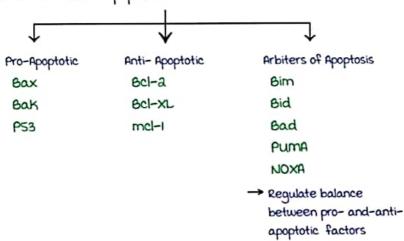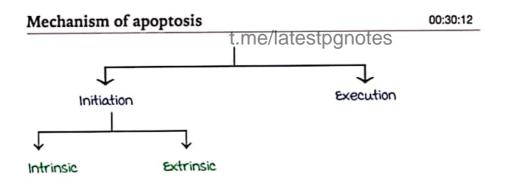
• 2 Enzymes required for Apoptosis

Caspases
→ Cleave protein near
   Aspartic acid resdues
→ Types:

Endonucleases
→ Produce internucleosomal cleavage of DNA
   ↓
180-200 base pairs
DNA fragments

Initiator   Executioner

Caspases   Caspases

8 → Extrinsic   3 → most Important

9 → intrinsic   6

10   7

Active space

- On PAGE (Poly Acrylamide Gel Electrophoresis)

↓

1000 BP
800
600

} Step ladder pattern

- Factor involved in Apoptosis:

Pro-Apoptotic	Anti- Apoptotic	Arbiters of Apoptosis
Bax	Bcl-2	Bim
Bak	Bcl-XL	Bid
P53	mcl-1	Bad
		PumA
		NOXA

→ Regulate balance between pro- and-anti-apoptotic factors

Mechanism of apoptosis   00:30:12

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Initiation   Execution

Intrinsic   Extrinsic

Intrinsic pathway

- AKA mitochondrial Pathway
- m.c organelle affected in apoptosis – mitochondria
- Occurs in 90% of times
- Normal cells have : Bcl2, Bcl-XL, mcl-1 in the outer
  membrane of mitochondria, cytosol, ER
  ↓
  maintain permeability of cell
  ↓
  No leakage of cytochrome C
  ↓
  No apoptosis
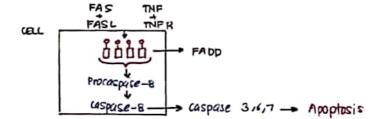
Active space

DNA damage →
Radiation
Infection

Activate the BH3 only sensors/arbiters of apoptosis
bim, bid, bad, PUMA, NOXA

↓

shift the balance towards pro-apoptotic

↓

Formation of bax-bak channel between inner and
outer mitochondria membrane.

↓

Leakage of cytochrome C

↓

Cyt.c-APAF-I (apoptosis activating factor-i)

↓

Apoptosome

↓

Activate caspase 9

↓

Caspase 3, 6, 7

↓

Apoptosis

→ inhibitor of intrinsic pathway : IAP (inactivates procaspase 9)

Extrinsic Pathway

- AKA death receptor mediated pathway
- 10%

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- Cells with death receptors

→ FAS, CD-95

→ TNF Receptor

→ Innibitor of extrinsic pathway : FLIP (inactivates procaspase 8)

Macrophage induced elimination of apoptotic bodies   00:40:51

- Normal cell
  - → Phosphatidylserine
  - → Phosphatidyl ethanola-mine
    On inner membrane

- Apoptotic
  - → Protein move to outer membrane
    Phosphatidyl serine flip.

- Annexin V
  - → Identifies phosphatidayl serine on outer surface

Morphological features of apoptosis   00:44:41

1. Cell shrinkage (Earliest feature)
2. membrane blebs
   ↓
   Pinch off
   ↓
   Apoptotic body

3. Nuclear chromatin condensation (most characteristic feature)
4. Plasma membrane is intact
   ↓
   No inflammation

Necrosis		Apoptosis	
1.	Passive	1.	Active
2.	Group of cell	2.	Single cell death
3.	Cell – swelling	3.	Cell – shrinking
4.	Plasma membrane damage	4.	Intact
		5.	⊖
5.	Inflammation ⊕	6.	Physiological + pathological
6.	Always Pathological	7.	Annexin V, CD95
7.	No marker	8.	Step ladder pattern
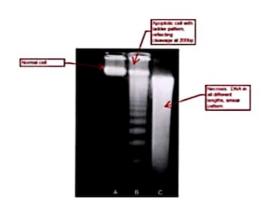
Active space

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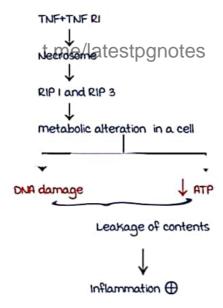
Necroptosis and pyroptosis   00:51:16

Necroptosis

- Hybrid of Necrosis +Apoptosis
- mechanism like apoptosis, but morphological features are like necrosis
- Programmed Necrosis
- Caspase independent
- Protein : RIP I and RIP 3
- Starts like extrinsic pathway:

TNF+TNF RI
↓
Necrosome
↓
RIP I and RIP 3
↓
metabolic alteration in a cell

DNA damage   ↓ ATP

Leakage of contents
↓
Inflammation ⊕

- Example :   Physiological
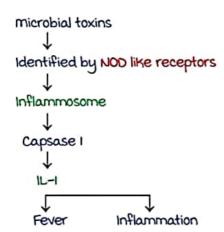
    → Formation of mammalian bone growth plate

    Pathological

    → Acute pancreatits

    → Reperfusion injury

    → Neurodegenerative disease like Alzheimer's

Pyroptosis

- Pyrogen induced apoptosis
- In certain infections

microbial toxins
↓
Identified by NOD like receptors
↓
Inflammosome
↓
Capsase I
↓
IL-I
┌──────────┴──────────┐
↓   ↓
Fever   Inflammation

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Active space

INTRACELLULAR ACCUMULATIONS

Free radial injury   00:00:15
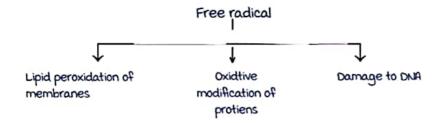
- Definition
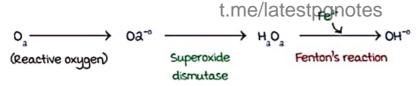
  molecules with 1 or more unpaired electrons in their outermost orbit

- Examples

  $O2^{-o}$, OH^{-o}, H_2O_2, $OONO^{-o}$ etc.

- mechanism of injury

Free radical

- Lipid peroxidation of membranes
- Oxidtive modification of protiens
- Damage to DNA
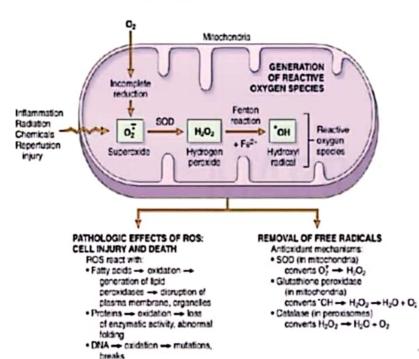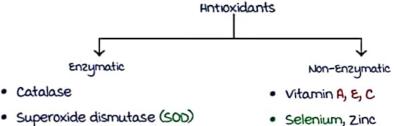
- mechanism of production of free radicals

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$$O_2 \longrightarrow O2^{-o} \longrightarrow H_2O_2 \xrightarrow{Fe} OH^{-o}$$

(Reactive oxygen)   Superoxide dismutase   Fenton's reaction

O₂

Mitochondria

GENERATION OF REACTIVE OXYGEN SPECIES

Incomplete reduction

Inflammation
Radiation
Chemicals
Reperfusion
injury

O_2^- SOD H_2O_2 Fenton reaction $^•OH$ Reactive oxygen species

Superoxide   Hydrogen peroxide   + Fe²⁺   Hydroxyl radical

PATHOLOGIC EFFECTS OF ROS: CELL INJURY AND DEATH
ROS react with:
- Fatty acids → oxidation → generation of lipid peroxidases → disruption of plasma membrane, organelles
- Proteins → oxidation → loss of enzymatic activity, abnormal folding
- DNA → oxidation → mutations, breaks

REMOVAL OF FREE RADICALS
Antioxidant mechanisms:
- SOD (in mitochondria) converts O_2^- → H_2O_2
- Glutathione peroxidase (in mitochondria) converts $^•OH$ → H_2O_2 → $H_2O + O_2$
- Catalase (in peroxisomes) converts H_2O_2 → $H_2O + O_2$

Active space

→ **most potent** free radical is OH^{-o}

• Antioxidants

Free radical scavengers

Antioxidants
├── Enzymatic
│   • Catalase
│   • Superoxide dismutase (SOD)
│   • Glutathione peroxidase
└── Non-Enzymatic
    • Vitamin A, E, C
    • Selenium, Zinc
    • Serum proteins
    ├── Iron binding
    │   - Lactoferrin
    │   - Transferrin
    └── Copper binding
        - Ceruloplasmin

- Vitamin A is not an antioxidant in **vitreous humor** of eye.

Enzymatic

I. SOD

SOD
├── SOD-1
│   • Cu-zn SOD
│   • Present in **cytosol**
└── SOD-2
    • mn - SOD
    • Present in **mitochondria**
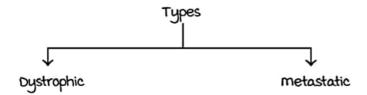
- Brain is protected from free radial injury by SOD-1
  ∴ mutation in SOD_1 ⟹ **Amylotrophic lateral sclerosis** of brain

- Function of SOD : Inactivates superoxide free radical

2. Catalase

- Present in **peroxisome**
- Inactivates H_2O_2

3. Glutathione peroxidase
- Present in **both** cytosol and mitochondria
- Inactivates **both** H_2O_2 + OH^- free radical

Active space

Pathologic calcification and types   00:11:27

Deposition of abnormal amount of calcium in the body with small amount of other minerals such as manganese

```
                    Types
                      |
        ┌─────────────┴─────────────┐
        ↓                           ↓
   Dystrophic                  metastatic
```
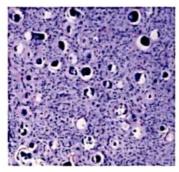
a) Dystrophic calcification

– Occurs in dead tissue

– No abnormality of calcium metabolism

– Serum Ca^{2+} level – Normal

– Examples:

    R – Rheumatic vegetations

    A – Atheromatous plaque

    T – Tubercular lymphnode

Other examples:

- Dead parasites   t.me/latestpgnotes
- monckeberg's medial calcific sclerosis
- Psamomma bodies – seen in

    i) Papillary carcinoma – thyroid

    ii) Papillary renal cell carcinoma (RCC)

    iii) meningioma

    iv) Serous cystadenocarcinoma ovary

Psamomma bodies

b) metastatic calcification
  - Occurs in living tissue
  - Serum Ca^{a+} level - $\uparrow\uparrow$ ⇒ Hypercalcemia
  - Abnormal calcium metabolism
  - Examples:
    • Sarcoidosis
    • Vitamin D related disease
    • Parathyroid diseases
    • Bone disease like Multiple Myeloma
    • milk alkali syndrome

- Note:
i) Calcification begins in mitochondria
   Except kidney – where it starts in the basement membrane of
   renal tubules.
ii) Sites of metastatic calcification:
   - Lung alveoli (most common)
   - Kidney
   - Gastric mucosa
iii) Stains used for calcium:
   - Von kossa stain
   - Alkaline red stain
iv) Tetra cycline labelling
   - Used to detect bone mineralization

Warning : Not all points are covered in the notes, especially conceptual
explanations. Please use the notes in conjunction with marrow Edition 4
videos.

Intracellular accumulations   00:19:14

1. Glycogen deposits
   - Seen in Glycogen storage disorders
   - Seen as Armanni Ebstein lesion in diabetic nephropathy in kidney
     tubules
2. Fat
   - Triglyceride deposits seen in fatty liver
   - Cholesterol deposits seen in xanthomas, atherosclerosis

Active space

3. Protein deposits
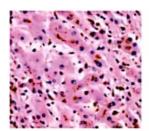
- Deposits as Russel bodies in plasma cells

- Seen in multiple myeloma

4. Pigment deposits
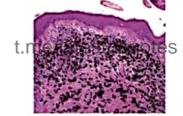
a) Lipofuscin

- Produced by lipid peroxidation of membranes

- Also known as ageing/wear and tear pigments

- Brown atrophy of liver and heart

- Perinuclear brown pigments.

b) melanin

- Derived from tyrosine

- Appears black in colour

- Special stain → masson Fontanna

- Marker → HMB-45, melan-A, S-100
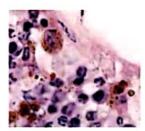
Lipofuscin   melanin
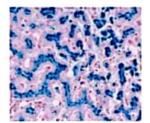
b) Hemosiderin

- Deposited in conditions with iron overload

- Pigment colour → Golden yellow/Brown

- Special stain → Prussian blue/Perl's

Hemosiderin   Perl's stain (Blue coarse granules)

Active space

Cellular ageing

Theories:

i) Free radical injury (most commonly accepted)

ii) ↑ cross linking of collagen

iii) DNA damage

iv) Telomere – Telomerase hypothesis

Telomeres

- Short repeat sequences of nucleotides present at the ends of chromosome.

- Sequence: TTAGGG (usually)

- Called as biological clocks

Telomere Shortening

↓

Cellular Ageing

Telomerase

- An enzyme which helps in synthesis of telomeres

- Inhibits cellular ageing

- Also called as immortality gene

- Seen in • Germ cell (good activity)

   • Somatic cell (less or no activity)

• mechanism of carcinogenesis

   - Limitless replicative potential

   (i.e. constitutive activation of telomerase)

• Hayflick limit

   - Normal cell undergoes 60–70 cell divisions in their life span

• werner syndrome

   - Defect in DNA helicase

   - Premature ageing

- Werner's syndrome
    - MEN-I syndrome

Sirtuins, autophagy   00:39:06

I. Sirtuins

    - ↑ life span/longevity
    - NAD dependent protein deacetylase
    - ↑ life span of cells by improving insulin resistance

    Sirtuin levels can be increased by -
    - Calorie restriction
    - Wine consumption
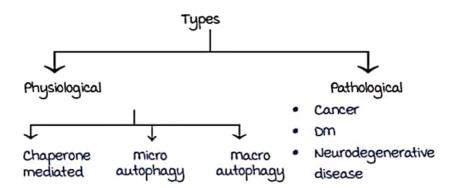
    Sirtuins have a role in -
    - Diabetes mellitus (DM)
    - Cancer
    - Ageing

a. Autophagy

    t.me/latestpgnotes
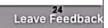
    - Self eating
    - Eats its own contents
    - Responds to nutrient deprivation

Types

Physiological

Chaperone mediated | micro autophagy | macro autophagy

Pathological
- Cancer
- DM
- Neurodegenerative disease

    - marker for autophagy

LC-3 (microtubule associated light chain)

Active space
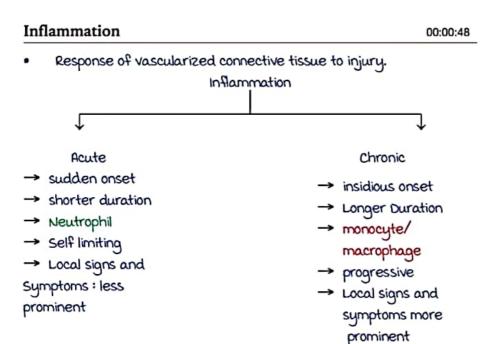
Important stains in pathology   00:45:05

Substance/Cell/Condition	Stain
1. most common stain in Histopathology	Hematoxylin and Eosin
2. Lipid/Fat	– Oil red O – Sudan black
3. Glycogen PAS positive substances: i) Glycogen ii) Basement membrane iii) mucin iv) Fungi Basement membrane with PAS stain Intact Affected ↓ ↓ Insitu Invasive	PAS positive
4. Iron/Hemosiderin	Perl's/Prussian blue
5. Calcium	– Von Kossa – Alzarine Red
6. melanin	masson Fontana
7. Collagen	masson Trichrome (mT)
8. Copper	Rhodanine, Orcein, Rubeanic acid
9. Fungi	– Silver methenamine/Gomori methenamine (GmS) – PAS positive
10. Elastin Fibres	Van Geison
11. Reticulin Fibres	Silver Stain
12. H. pylori	Warthin Starry Silver
13. Amyloid	Congo Rea
14. mycobacterium Tuberculosis	Zeihl Neelson (ZN)
15. M. Leprae	Fite
16. Cryptococcus	India Ink
17. mucin	mucicarmine Alcian Blue
18. mast cell	Toluidine Blue

Active space

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ACUTE INFLAMMATION

Inflammation   00:00:48

- Response of vascularized connective tissue to injury.

Inflammation

Acute	Chronic
→ sudden onset	→ insidious onset
→ shorter duration	→ Longer Duration
→ Neutrophil	→ monocyte/ macrophage
→ Self limiting	→ progressive
→ Local signs and Symptoms : less prominent	→ Local signs and symptoms more prominent

- Acute inflammation produces exudates.

Exudate	Transudate
1. Inflammatory edema	1. Non Inflammatory edema
2. Specific gravity < 1.020	2. Specific gravity < 1.012
3. Rich in cells and proteins	3. Poor in cells and proteins
4. LDH : high	4. LDH : low
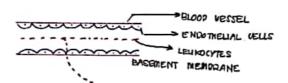
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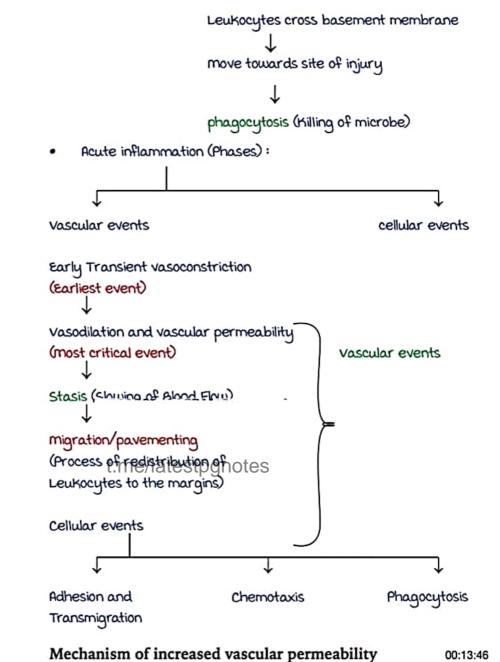
Acute inflammation   00:04:36

- 4 cardinal signs of acute inflammation (by Celsus) :
- Rubor – Redness
- Dolor – Pain
- Calor – Heat
- Tumor – swelling

- Virchow gave the 5th sign of Acute inflammation : Functio laesa

mechanism of inflammation

BLOOD VESSEL
ENDOTHELIAL CELLS
LEUKOCYTES
BASEMENT MEMBRANE

Active space

Leukocytes cross basement membrane
↓
move towards site of injury
↓
phagocytosis (Killing of microbe)

- Acute inflammation (Phases):

Vascular events   cellular events

Early Transient vasoconstriction
(Earliest event)
↓
Vasodilation and vascular permeability
(most critical event)   Vascular events
↓
Stasis (Slowing of Blood Flow)
↓
migration/pavementing
(Process of redistribution of
Leukocytes to the margins)

Cellular events

Adhesion and   Chemotaxis   Phagocytosis
Transmigration

Mechanism of increased vascular permeability   00:13:46

I. Endothelial cell contraction
    → occurs in post capillary venules
    → immediate transient response (lasts for 15-30 min)
    → Factors: Histamine, leukotrienes.
2. Endothelial cell retraction
    → occurs in venules and capillaries
    → mediators : IL-1, TNF-α
    → delayed sustained response

3. Direct Endothelial injury
    → Acts on capillaries, venules and arterioles

→ can be

Severe injury	**mild injury**
→ Due to severe sunburn, Or chemicals	→ Endothelial cells undergo apoptosis
↓	↓
Endothelial cells will undergo necrosis and detachme	Leakage starts (After some time)
↓	↓
Leakage of fluid (Starts immediately)	Delayed sustain response
↓	
Continue until new Cells regenerate	
↓	
Immediate sustained response	
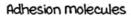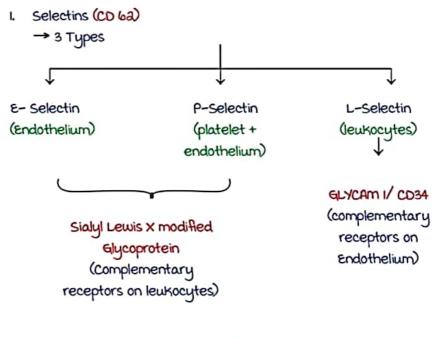
4. Increased transcytosis
    → Passage of fluid through the channels which are formed in endothelial cell cytoplasm.
    → mediators : VEGF
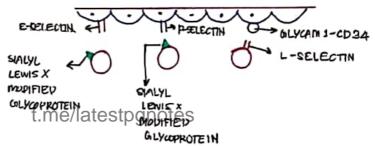
Cellulars events and adhesion molecules   00:21:45

Rolling → selectins
(Loose attachment)

Adhesion → integrins
(Firm attachment)

Transmigration → CD31/PECAM 1
→ movement across basement membrane

Active space

Adhesion molecules

1. Selectins (CD 62)
   → 3 Types

| ε- Selectin (Endothelium) | P-Selectin (platelet + endothelium) | L-Selectin (leukocytes) |

Sialyl Lewis X modified Glycoprotein (Complementary receptors on leukocytes)

GLYCAM I/ CD34 (complementary receptors on Endothelium)

2. Immunoglobulins

   → ICAM-1
   (Intercellular adhesion molecule-1)
   → VCAM-1
   (vascular adhesion molecule-1)

   present on endothelium

3. Integrins

   → β 2-integrin (CD 11/CD 18)
                  (LFA1/ MAC 1)

   → β 1-integrin (VLA-4)

   present on leukocyte

Adhesion

Active space

4. CD31/PECAM I (Platelet endothelium cell adhesion molecule-I)
→ mediates transmigration (movement of leukocyte across the basement membrane)

• Adhesion molecules:

	Endothelium	Leukocyte	Function
I.	E-Selectin	sialyl lewis x	
a.	P-Selectin	modified glycoprotein	Rolling
3.	GLYCAM I – CD34	L – Selectin	
4.	ICAM – I	β2 – integrin	Adhesion
5.	VCAM – I	β1 – integrin	

Mechanism of appearance of adhesion molecules   00:35:21

I. Redistribution
→ Applicable of P-Selectin
→ P-Selectin is present on Weibel Palade body of endothelium
→ During inflammation → mediators like histamine, thrombin, PAF

↓

Release of P-Selectin to the surface of endothelium

a. Induction
→ Fresh synthesis of certain adhesion molecules.
• ICAM-I
• VCAM-I
• E-Selectin
→ mediated by IL-I, TNF-α

3. ↑ Avidity of Binding
→ integrins present on leukocytes
→ ↑ strength of binding

Chemotaxis   00:39:59

• movement of neutrophil in the direction of a chemical stimulus towards site of inflammation

Chemotactic factors

Exogenous
→ Bacterial cell wall proteins like N-Formyl methionine
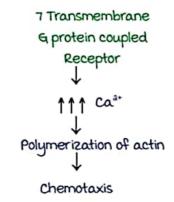
Endogenous
I. C5a
a. LTB4
3. IL-8

- mechanism :

7 Transmembrane
G protein coupled
Receptor
↓
↑↑↑ Ca^{2+}
↓
Polymerization of actin
↓
Chemotaxis
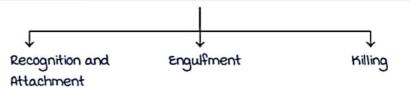
Phagocytosis   00:44:32

Recognition and   Engulfment   Killing
Attachment
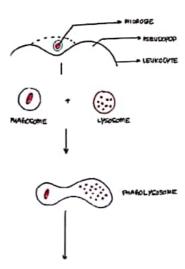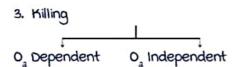
I. Recognition and Attachment
→ 3 Receptors on leukocytes
1. mannose receptor
2. Scavenger Receptor   }   Helps to identify the bacteria
3. mAC-1 Receptor.

- Opsonisation
→ Coating of microbe so that it is easily phagocystosed
→ Opsonins :
1. Fc fragment of IgG
2. C3b
3. Serum proteins like fibrinogen, CRP etc.
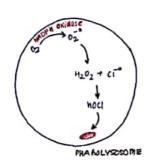
2. Engulfment

3. Killing

O_2 Dependent O_2 Independent

Oxidative burst (O_2 dependent + Killing)
→ H_2O_2 – Halide : most effective
        bacterial Killing system.

→ O_2 independent Killing
– mediated by lysosomal enzymes: Lactofferin, lysozyme,
  bactericidal, permeability, increasing protein.

Leukocyte function defects   00:54:28

I. LAD I (Leukocyte Adhesion Defect-I)
   → Autosomal recessive (AR) condition
   → pathogenesis: defect in β2 integrin
   → Clinically I. Recurrent Infections
                 2. Delayed separation of umbilical stumps
                 3. Delayed wound healing.

2. LAD 2
   → Pathogenesis : mutation in sialyl Lewis x modified glycoprotein

3. Chronic Granulomatous Diseases (CGD)
   → CGD → XLR (75%)
            ↳ AR (25%)
   → Defect : deficiency of NADPH Oxidase
                    ↓
   Defective O_2 dependant Killing
   → Clinically : Recurrent infections with catalase positive
     organisms
   → Test : Nitro Blue Tetrazolium test (NBT)

4. Chediak Higashi Syndrome
   → AR
   → Pathogenesis : mutation of LYST protein required for
                    phagolysosome fusion
   → Clinically : Fever
                  Recurrent Infections
                  Albinism
                  Deafness
                  Thrombocytopenia
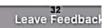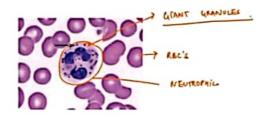
Active space

→ Peripheral smear : Giant granules in neutrophills
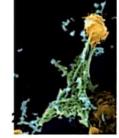
Neutrophil Extracellular Traps (NET)   01:03:56

- Extracellular fibrillar meshwork produced by neutrophils at site of infection
- Provide a high concentration of anti - microbial substance at the infection site

$$\downarrow$$

prevents the spread of microbes
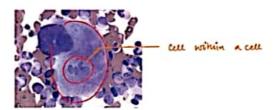
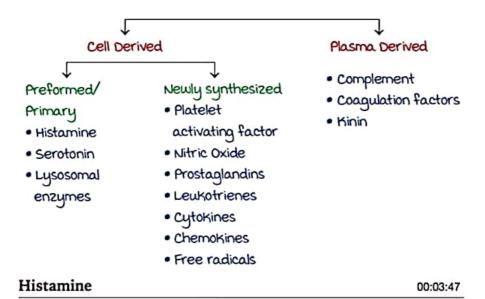- Arginine is involved in the production of NET

Emperipolesis   01:06:41

- infect cell within cytoplasm of another cell
- Differential diagnosis : Phagocytosis
- cell inside remain viable
- cell can also exit without any structural or morphological change
- Example: 1. Rosai Dorfman syndrome
  2. Hematolymphoid disease like CLL
  3. NHL

cell within a cell

Active space

MEDIATORS OF INFLAMMATION

Cell Derived | Plasma Derived

Plasma Derived
- Complement
- Coagulation factors
- Kinin

Preformed/ Primary
- Histamine
- Serotonin
- Lysosomal enzymes

Newly synthesized
- Platelet activating factor
- Nitric Oxide
- Prostaglandins
- Leukotrienes
- Cytokines
- Chemokines
- Free radicals

Histamine   00:03:47

- Richest source – Mast cell
- Stain for mast cells – Toluidine Blue
- Earliest to be released
- Functions:
  - Vasodilation
  - Vasoconstriction in larger vessels
  - ↑ Vascular permeability
- Triggers: C3a, C5a, IL-1, IL-2, Physical agents-heat, trauma etc.

Serotonin, lysosomal enzyme   00:06:13

- Serotonin :
- Richest source → Basophils
- Also seen in Enterochromaffin cells of GIT
- Function → Same as histamine
- Lysosomal enzymes:
- Seen in granules of neutrophils

Primary/Azurophilic granules
- MPO (myeloperoxidase)
- BPI (Bacterial permeability increasing protein)
- Lysozyme
- Neutral proteases
- Defensins
- Phospholipase A_2
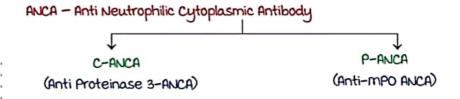
Secondary granules
- small, fine
- Lysozyme
- Lactoferrin
- Phospholipase A_2
- Gelatinase
- Alkaline phosphatase

Active space

ANCA – Anti Neutrophilic Cytoplasmic Antibody

```
                    C-ANCA                          P-ANCA
            (Anti Proteinase 3-ANCA)            (Anti-MPO ANCA)
```

Platelet activating factor   00:11:44

- Sources: all leukocytes & platelets/mast cells

- most potent inflammatory mediators

- Functions: ↑ platelet Aggregation
  eternalsoul_494@yahoo.com
  - Vasodilation

  - Vascular permeability

  - Bronchospasm

Arachidonic acid metabolites   00:13:23

- 20 carbon poly unsaturated fatty acid

```
                    Phospholipids
                         │ Phospholipase
                         ↓
                  Arachidonic Acid (AA)

            Cyclooxygenase │ Lipoxygenase
```

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PGI_2	TXA_2	PGD_2	TXA_2	TXA_2
(prostacyclin)	(Thromboxane	PGE_2	(Thromboxane	(Thromboxane
	A_2)	$PGF_2\alpha$ } Prostaglandins	A_2)	A_2)

Cyclooxygenase Pathway: COX-1

COX-2 → Inducible

AA Cyclooxygenase → PGG2 → PGH2

```
                      Prostaglandins
    PGI₂                                         TXA₂
(prostacyclin)    PGD₂    PGE₂    PGF₂α      (Thromboxane)
```

- vasodilation
- platelet aggregation
- role in inflammation

- can cause – vasospasm
              – Bronchospasm

- vascular permeablity

- vascular permeability
- Platelet aggregation
- Hemostasis
- No role in inflammation

$PGE_2 \rightarrow$ fever, pain
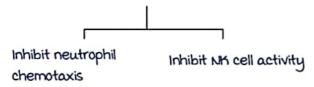
PGD_2 & $PGF_2\alpha \rightarrow$ Neutrophil, chemotaxis

$PGF_2\alpha \rightarrow$ Helps in uterine & bronchial smooth muscle contraction

Lipoxygenase pathway:

AA $\xrightarrow{\text{lipoxygenase}}$ SGPETE

$$\downarrow$$

LTAG $\rightarrow$ LTB4 $\rightarrow$ Chemotaxis

LTC_4
$\downarrow$ } • ↑ vascular PERMEABILITY
LTD_4 • Bronchospasm
$\downarrow$
LTE_4

- Lipoxins — Anti inflammatory action

        |
    ┌───┴───┐
Inhibit neutrophil   Inhibit NK cell activity
chemotaxis

Applications on arachidonic acid pathway   00:23:18

- Steroids: – Act on phospholipase
                    – Broad spectrum anti inflammatory drugs

- Leukotriene Antagonists:
                    – montelukast, Zafirlukast $\rightarrow$ Bronchodilation
                    ∴ used for Bronchial Asthma

- Aspirin & other NSAID's:
                    – Inhibit COX1 & COX2

Chemokines   00:26:10

- They are small molecules specific for chemotaxis of particular cells.
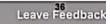
1) C-x-C: α Chemokine
- a cystine resdue. X-Any other amino acid other than cystine
- specific for Neutrophil.
  Eg: IL – 8

2) C-C: β Chemokine
- 2 cystine residue together
- Specific for all leucocytes except Neutrophils

Active space

Eg: Eotaxin,   MCP-1,   MP-1α
         ↓   ↓   ↓
       eosin   monocytes   monocyte, macrophages

3) C chemokine : Chemokine
- Specific for lymphocytes
- eg: Lymphotaxin

4) CX3C: Chemokine
- specific for monocyte — Fractalkine

• Chemokine receptors like — CXCR4 ⎫
                                                        ⎬ act as co-receptors for HIV
                                      CCR5 ⎭

Nitric oxide   00:30:53

- Colourless & odourless gas
- Aka EDRF (endothelium derived relaxation factor)
- produced from Argnine

                          Nitric Oxide synthetase
- Arginine ————————————————→ NO
                                    C GMP

-NO synthetase ——┬—— e NOS (endothelial)
                              ├—— n NOS (neuronal)
                              └—— iNOS (inducible)

Function :   - Vasodilator
                    - Smooth muscle relaxation
                    - Inhibit platelet aggregation
                    - Per Oxynitrite (OONO-o) = Free radical — microbicidal

Cytokines   00:34:24

-    Acute Inflamation → IL 1 ⎫ Produce systemic effects of inflammation
                              → IL6   ⎬
                              → TNFα ⎭ Fever, sleep, ESR, appetite

• most important in SIRS, Cancer Cachexia — TNFα

Active space

- Fever – IL-I

ii) endothelial activation

iii) Chemotaxis – IL 8

- Chronic Inflammation – IL 12

                    IL 17

                    IFN

- IFN – most important for Granuloma formation
- most fibrogenic cytokine- TGFβ
- Anti inflammatory cytokines – IL 4, 6, 10, 13, TGF – β
- Both Pro & Anti Inflammatory – IL 4 & 6

Plasma derived mediators   00:38:48

i) Complement system : series of 20 proteins present in the plasma.

- Activated by 3 pathway ┬ Classical – Starts with activation of C_1
                            ├ Alternate – Starts with C_3
                            └ Lectin/mannose binding – starts with C_1

                        Activated by

- Classical pathway   ⟶   Ag-Ab complex
- Alternate pathway   ⟶   • Cobra venom
                                   • Lipopolysaccharide
                                   • Endotoxin
- Lectin pathway   ⟶   mannose binding

- most critical step in complement cascade → Activation of C3
- Final step in complement cascade → C5b-9 → membrane Attack
                                         complex
- Function: • Anaphylatoxins – C3a, C5a
                • Opsonins – C3b
                • Killing of microbes – C5b-9 (mAC)
                • Chemotaxis – C5a

Active space

Complement protein deficiency	Disease caused
C_1 Inhibitor (C_1 INH) $\rightarrow$	Hereditary Angioneurotic edema
C_2 or early components of $\rightarrow$ complement	risk of SLE
C_3 or late components of $\rightarrow$ complement	risk of pyogenic infertion
Regulators of complements $\rightarrow$ CD_{55}, CD_{59}	Paroxysmal Nocturnal Hemoglobinuria

ii) Kinin cascade: produce Brady Kinin

Pre Kallikrein   Factor XII or

$\xrightarrow{\hspace{2cm}}$ Kallekrein

Hageman factor

$\downarrow$

Brady Kinin $\longleftarrow$ High molecular weight Kininogen

Function: Brady Kinin: $\rightarrow$ • Pain

• $\uparrow$ Vascular permeablity
• Vasospasm
• Bronchospasm

iii) Factors in coagulation cascade

• Fibrinogen $\rightarrow$ opsonin
• Thrombin $\rightarrow$ Redestribution of E-Selection
• Fibrino peptides $\rightarrow$ Chemotaxis $\rightarrow$ Neutrophil

Active space

CHRONIC INFLAMMATION

- Characterized by :

1. Infiltration of tissue by mononuclear cells

   Eg : Lymphocytes
   Plasma cells
   macrophages

2. Tissue Destruction

3. Attempts at healing by Angiogenesis/ Fibrosis

Macrophage   00:02:14

- Tissue Specific monocytes

- Tissue Resident macrophages :

  1. Liver → Kupffer cells
  2. Brain → microgila
  3. Spleen → Sinus Histiocytes
  4. Lymph node → Sinus Histiocytes
  5. Kidney → mesangial cells
  6. Placenta → Haufbauer cells
  7. Lung → Pulmonary Alveolar macrophages (Dust Cells)
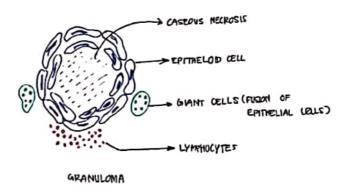
Active space

macrophage

Induced by	Induced by
IFN-γ	IL-4
Endotoxin	IL-13
produce : IL-1, 6, 12	produce : IL-10, TGF-β
↓	↓
m1	m1
↓	↓
Classically Activated	Alternatively Activated

Classically Activated →
- Reactive Oxygen Species
- NO
- Lysosomal Enzymes

1. Kill the bacteria
2. Tissue destruction

Alternatively Activated →
1. Anti inflammatory action
2. Fibrosis

Warning : Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with marrow Edition 4 videos.

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Granulomatous inflammation   00:06:33

- Granuloma : Collection of modified activated macrophages (Epitheloid cells), surrounded by a collar of lymphocytes and sometimes Giant cells.

- CASEOUS NECROSIS
- EPITHELOID CELL
- GIANT CELLS (FUSION OF EPITHELIAL CELLS)
- LYMPHOCYTES

GRANULOMA

Active space

Types of Giant cells   00:11:00

1. Foreign Body Giant cells
    → Seen in talc, suture material etc.
    → Haphazard Arrangement of Nuclei

2. Langhans Giant Cells
    → Horse shoe arrangement of nuclei
        ↓
    Characteristic in TB

3. Touton Giant Cells
    Nucleus in center, surrounded by fat droplets.
    in Xanthoma

4. Tumor Giant cells

5. Reed Sternberg cell

6. Warthin Finkeldey Giant cells
    → seen in measles.

Mechanism of giant cells formation   00:14:30

*   Granuloma Formation → Type IV hypersensitivity Reaction
    Antigen acts upon CD4 TH1 cells
        ↓
    IFN - γ → most important cytokine
        ↓
    macrophage
        ↓
    Activated macrophage
        ↓
    Granuloma Formation

*   List of Granulomatous Diseases :

1. TB
2. Sarcoidosis
3. Leprosy
4. Syphilis
5. Chronic Granulomatous Diseases
6. Cat Scratch Diseases
7. Crohn's Diseases
8. Wegner's Granulomatosis
9. Berylliosis
10. Churg Strauss Syndrome

Active space

Granuloma

Immune Granuloma
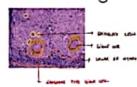
Foreign Body Granuloma
→ Seen in talc, suture
material etc

- Types of immune Granuloma :
  1. Caseating Granuloma
     → TB
     → Histoplasmosis
     → Coccidioidomycosis
     → Syphillis
  2. Non Caseating Granuloma
     → TB
     → Sarcoidosis
     → Crohn's Diseases
     → Hodgkins Lymphoma
  3. Naked Granuloma
     → Sarcoidosis (absence of lymphatic collar)
  4. Stellate Granuloma (Star Shaped)
     → Cat Scratch Disease
  5. Durk Granuloma → Plasmodium falciparum
  6. Doughnut Granuloma/Fibrin granuloma → Q Fever
  7. Eosinophilic Granuloma → churg strauss syndrome
  8. Necrotising Granuloma → wegener's granulomatosis
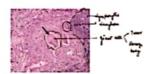
Histopathological images   00:21:59
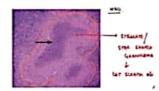
1. Granuloma : Langhans Types Giant cell

2. Various cells seen on H&E biopsy

3. Stellate/ star shaped granuloma
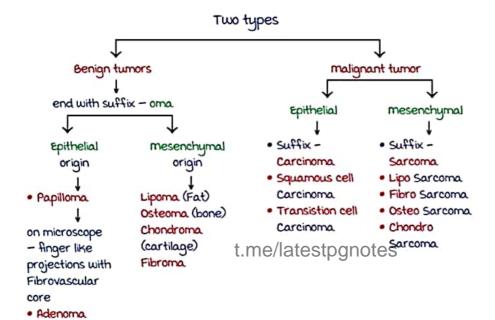
NEOPLASIA – BASIC CONCEPTS - 1

Neoplasia – nomenclature   00:01:27
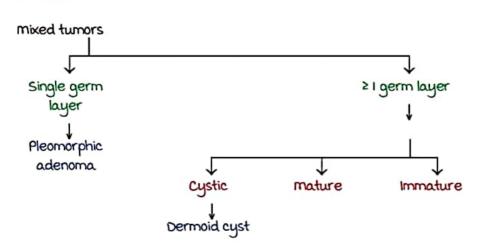
- Neoplasia – Neo – New
          Plasia – growth

- Definition – Any new autonomous growth (independent of growth factors).

Two types

Benign tumors   malignant tumor

end with suffix – oma   Epithelial   mesenchymal

Epithelial   mesenchymal   • Suffix –   • Suffix –
origin   origin   Carcinoma   Sarcoma
                                     • Squamous cell   • Lipo Sarcoma
• Papilloma   Lipoma (Fat)   Carcinoma   • Fibro Sarcoma
                  Osteoma (bone)   • Transistion cell   • Osteo Sarcoma
on microscope   Chondroma   Carcinoma   • Chondro
– finger like   (cartilage)   Sarcoma
projections with Fibroma
Fibrovascular
core
• Adenoma

Malignancies which end with – oma and mixed tumors 00:06:02

- Seminoma
- Lymphoma
- Chordoma
- Chloroma
- melanoma

mixed tumors

Single germ layer   ≥ 1 germ layer

Pleomorphic adenoma

                        Cystic   mature   Immature

                        Dermoid cyst

Active space

Choriostoma and hamartoma, benign and malignant   00:09:29

Choriostoma	Hamartoma
• Normal tissue in abnormal location	• Abnormal tissue in normal location
• Ectopic rest of normal tissue	• Tissue is disorganised/ haphazard
	• e.g. Pulmonary hamartoma
• e.g. : Pancreatic tissue in stomach	• Shows – clonal chromosomal rearrangements – so considered as tumors.

Benign	malignant
• Do not show Anaplasia	• Anaplasia present
• Slow growing	• Rapidly growing
• Encapsulated, local invasion absent	• Non decapsulated, local invasion – Present
• metastasis absent	• metastasis Present

Tumors – property of anaplasia   00:13:52

- Anaplasia – Lack of differentiation – Hallmark of malignancy (cells differ from original cells both in structure and function).

Anaplastic cell properties

- Pleomorphism – variation in size & shape of cells
- ↑ N/c ratio – 1:1 (in normal cells – N/c ratio – 1:4 – to 1:6)
- Hyperchromatic Nuclei – (Nucleus becomes almost the size of cytoplasm, densely basophilic – chromatic)
- Prominent nucleoli
- Loss of Polarity – nuclei can be present anywhere in cell (in normal cell nucleus is present either in lower or upper pole)
- Abnormal mitosis – Sign of proliferation
  Tripolar mitosis – mercedes benz sign – ⊘

Normal cell   Anaplastic cell
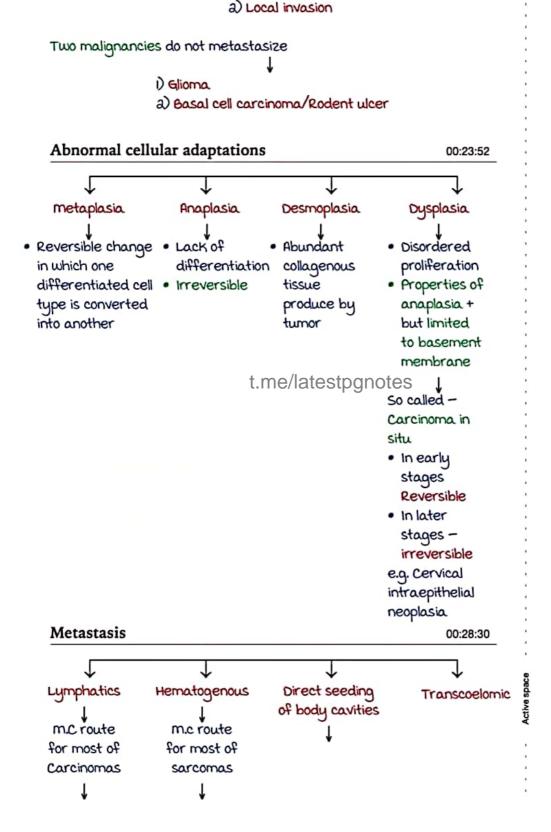
Tumors – other properties   00:19:49
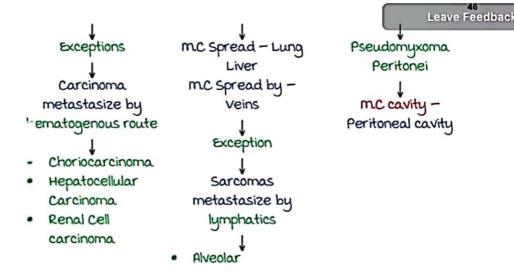
- Benign – tumors – slow growing – present for long time
- malignant tumors – Rapidly growing – occur in a short time

- most characteristic/ultimate feature to differentiate between benign and malignant tumors
  ↓
  1) metastasis
  2) Local invasion

Two malignancies do not metastasize
  ↓
  1) Glioma
  2) Basal cell carcinoma/Rodent ulcer

Abnormal cellular adaptations   00:23:52

metaplasia	Anaplasia	Desmoplasia	Dysplasia
↓	↓	↓	↓
• Reversible change in which one differentiated cell type is converted into another	• Lack of differentiation • Irreversible	• Abundant collagenous tissue produce by tumor	• Disordered proliferation • Properties of anaplasia + but limited to basement membrane

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So called –
Carcinoma in situ
- In early stages Reversible
- In later stages – irreversible

e.g. Cervical intraepithelial neoplasia

Metastasis   00:28:30

Lymphatics	Hematogenous	Direct seeding of body cavities	Transcoelomic
↓	↓	↓	
m.c route for most of Carcinomas	m.c route for most of sarcomas	↓	
↓	↓		

Active space

↓   ↓   ↓
Exceptions   m.c Spread – Lung   Pseudomyxoma
                              Liver   Peritonei
↓   ↓   ↓
Carcinoma   m.c Spread by –   m.c cavity –
metastasize by   Veins   Peritoneal cavity
hematogenous route
                              ↓
↓   Exception
- Choriocarcinoma   ↓
• Hepatocellular   Sarcomas
  Carcinoma   metastasize by
• Renal Cell   lymphatics
  carcinoma   ↓
                      • Alveolar

Tumors spread via cerebrospinal fluid

↓   ↓
medulloblastoma   Ependymoma
↓
goes to cauda equina
through CSF
↓
Called – Drop
metastasis to cauda
equina

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Tumors that undergo spontaneous regression
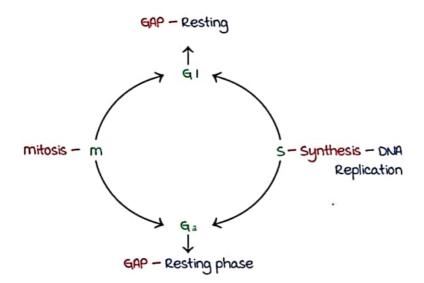
• Retinoblastoma
• Neuroblastoma
• Renal cell carcinoma
• Malignant melanoma
• Choroid carcinoma

Small, Round blue cell tumors of childhood

• Retinoblastoma – Flexner wintersteiner rosette seen
• Neuroblastoma – Homer wright rosette seen
• Nephroblastoma
• Hepatoblastoma
• Medulloblastoma
• Ewing's sarcoma
• PNET
• Rhabdomyosarcoma
• Lymphomas
• These tumors show Rosettes – cell are arranged around a space
  like flower.

Active space

Cell cycle

00:39:23
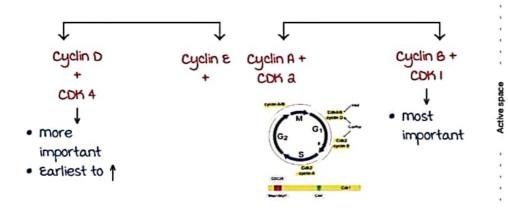
- Longest phase of cell cycle – Interphase
- most Radiosensitive Phase – G_2/m
- most Radioresistant Phase – S

Cell cycle regulators – cyclins, cyclin dependant kinases

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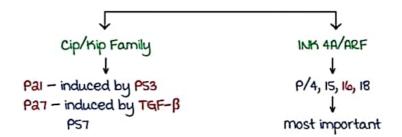
00:42:10

Cyclins		Cyclin dependant Kinases
D – Combine with	–	4, 6
E – Combine with	–	2
A – Combine with	–	2
B – Combine with	–	1

Cyclin D
+
CDK 4
↓
- more important
- Earliest to ↑

Cyclin E
+

Cyclin A +
CDK 2

Cyclin B +
CDK 1
↓
- most important

Active space
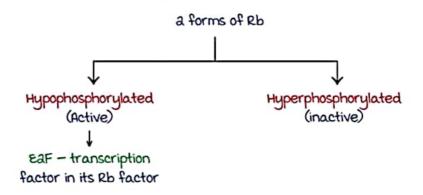
Cyclin dependant kinase – inhibitors

00:46:43

```
              Cip/Kip Family                    INK 4A/ARF
                   ↓                                ↓
      P21 – induced by P53              P/4, 15, 16, 18
      P27 – induced by TGF-β                    ↓
             P57                          most important
```
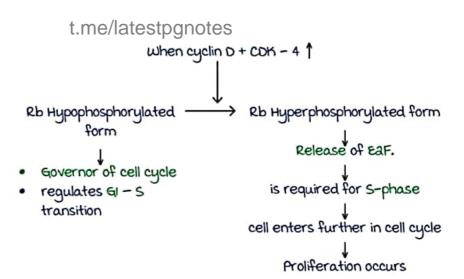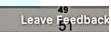
Role of Rb in cell cycle.

- Rb – Retinoblastoma gene on chromosome 13q 14

```
                         2 forms of Rb

        Hypophosphorylated              Hyperphosphorylated
            (Active)                        (inactive)
               ↓
        E2F – transcription
        factor in its Rb factor
```

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When cyclin D + CDK – 4 ↑

```
    Rb Hypophosphorylated    ⟶    Rb Hyperphosphorylated form
          form                              ↓
                                      Release of E2F.
            ↓                               ↓
•  Governor of cell cycle          is required for S-phase
•  regulates G1 – S                         ↓
   transition               cell enters further in cell cycle
                                            ↓
                                    Proliferation occurs
```

Active space

NEOPLASIA – BASIC CONCEPTS - 2

Molecular basis of cancer   00:00:10

1) Self sufficiency in growth signals (Oncogene)
2) Insensitivity to growth inhibitory signals (Tumor suppressor gene)
3) Evasion of apoptosis
4) Limitless replicative potential
5) Sustained angiogenesis
6) Invasion & metastasis
7) Altered cellular metabolism
8) Escape of immune recognition

Self Sufficiency in Growth Signals : Oncogenes
   Protooncogenes (Ⓝ genes) ➡   • Growth factors
                                      • Growth factor receptors
   | Translocation   • Signal transduction protein
   | Point mutation   • Nuclear transcription factors
   | Over expression   • Cyclins & CDK's
   | Amplification

   Oncogene (Cancer promoting gene)
        └──→ Oncoprotein ────→ Cancer

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Proto oncogenes   00:07:04

1) Growth Factors:
   a) Sis → Astrocytoma
   b) Hepatocyte Growth Factor → Hepatocellular carcinoma
   c) HST → Melanoma
   d) HST-1 → Osteosarcoma
   • Sis : PDGF-β
        - Over expression → Astrocytoma

2) Growth factor receptors:
   a) C-KiT $\xrightarrow[\text{mutation}]{\text{Point}}$ Gastro Intestinal Stromal Tumor
      (CD-117)

   b) EGF R ──┬─ EGF RI $\xrightarrow[\text{expression}]{\text{Over}}$ Adenocarcinoma Lung
      (epidermal growth │ (ERB-1)
      factor receptor)   └─ EGF R2 $\xrightarrow[\text{expression}]{\text{Over}}$ Breast & Ovarian Cancer
                            (ERD-2)

   c) RET $\xrightarrow[\text{mutation}]{\text{Point}}$ • medullary carcinoma of Thyroid
                        • MEN II Syndrome
   * Loss of function mutation in RET → Hirschsprung's disease

Active space
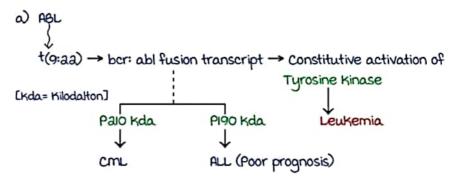
d) ALK ——chr2——→ • Anaplastic large cell lymphoma
(Anaplastic • Inflammatory myofibroblastic tumor
Lymphoma • Adenocarcinoma of lung
Kinase gene)

Proto oncogenes: signal transduction proteins   00:12:57

a) ABL

t(9:22) → bcr: abl fusion transcript → Constitutive activation of
Tyrosine Kinase

[Kda = Kilodalton]

P210 Kda   P190 Kda   Leukemia

CML   ALL (Poor prognosis)

b) RAS → mc oncogene mutated in human malignancy

— K-RAS ——Point mutation——→ Colon, Pancreas, lung cancer.

— H-RAS ——Point mutation——→ Bladder/ Kidney Tumors

— N-RAS ——Point mutation——→ melanoma

RAS Protein —— Active → GTP-RAS → Promote cell proliferation

—— Inactive → GDP-RAS → Inhibit cell proliferation

• Growth + Growth factor   →GTP-RAS   Signal transduction
  factor   receptor
                      GDP-RAS   Cell Cycle

• GAP (GTPase Activating protein) → Removes a phosphate group
                                        from GTP-RAS

                Stop cell proliferation ← GDP-RAS

• Point mutation in RAS → GAP cannot take out the phosphate
                              group

                cancer ← Cell Proliferation will continue

Active space
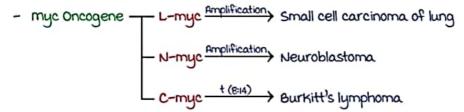
c) BRAF V600 $\xrightarrow{\text{mutation}}$
- Langerhans cell histiocytosis
- Papillary carcinoma of thyroid
- Hairy cell leukemia
- Astrocytomas
- Colon cancer

d) NOTCH $\longrightarrow$ ALL
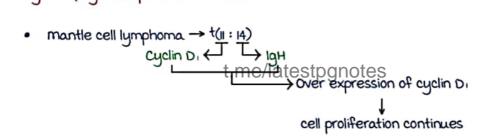
Proto oncogenes: nuclear transcription factor, cyclins & CDK'S 00:23:11

Nuclear Transcription Factors:

- myc Oncogene
  - L-myc $\xrightarrow{\text{Amplification}}$ Small cell carcinoma of lung
  - N-myc $\xrightarrow{\text{Amplification}}$ Neuroblastoma
  - C-myc $\xrightarrow{\text{t (8:14)}}$ Burkitt's lymphoma

Cyclins & Cyclin Dependent Kinases:

- mantle cell lymphoma $\rightarrow$ t(11 : 14)
  - Cyclin D_1 ← → IgH
  - → Over expression of cyclin D_1
  - ↓
  - cell proliferation continues

Warning : Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with marrow Edition 4 videos.

Insensitivity to growth inhibitory signals 00:26:48

Tumor Suppressor Genes [TSG]:
Loss of both copies of TSG $\rightarrow$ Cancer

1) Rb gene (Retinoblastoma)
   - Chr 13q 14
   - 2 forms
     - Active – Hypophosphorylated
     - Inactive – Hyperphosphorylated
   - mutation
     - Retinoblastoma
     - Osteosarcoma

   - It regulates G1 $\rightarrow$ S Transition in cell cycle

Active space

- Knudson's two hit hypothesis, LOH (loss of heterozygosity)
  ↓
  Both alleles of Rb should be
  mutated for Retinoblastoma
  to develop

- Rb ⌐ Familial → 1 copy of mutated allele by birth (Rr)
     │   and mutation after Birth (RR) (Heterozygous)
     └ Sporadic   (Homozygous)

* Homozygosity of mutant allele to develop Rb = LOH
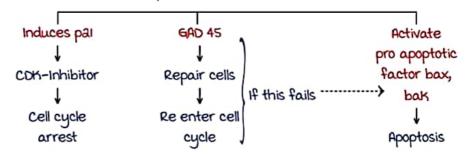
Tumor Supressor Gene (TSG): p53   00:33:38

- Chr 17p
- Mutation of p53 → Li fraumeni syndrome → Autosomal dominant
- a/k/a Guardian of Genome/molecular policeman of cells
- p53 mutation ⊕ > 50% human malignancy
- mc affected TSG in human malignancy = p53

Functions of p53:
- Damage from Ionizing Radiation

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  ↓
  Activation of p53

Induces p21	GAD 45		Activate
↓	↓		pro apoptotic
CDK-Inhibitor	Repair cells	If this fails ----→	factor bax,
↓	↓		bak
Cell cycle	Re enter cell		↓
arrest	cycle		Apoptosis

Important Tumor Supressor Genes

00:38:20

Gene	Chromosome	Tumor
p53	17p	Li fraumeni syndrome
Rb	13q	Retinoblastoma, osteosarcoma
NFI	17	Neurofibromas, meningiomas
NF2	22	Bilateral acoustic Neuroma/Schwannoma
BRCA I	17	Breast, ovarian cancer
BRCA 2	13	Male Breast cancer, Prostate cancer
WT I	11	Wilms Tumor
WT2	11	Wilms Tumor
PTEN	10	– Endometrial Cancer – Prostate cancer
VHL	3	– Clear cell Renal cell carcinoma – Cerebellar hemangioblastoma
APC	5	– Familial Adenomatous Polyposis – Adenocarcinoma colon

Limitless replicative potential, evasion of apoptosis

00:42:43

Limitless Replicative Potential:

- Telomerase – enzymes that synthesise Telomere
- Constitute activation of Telomerase – Development of cancer

Evasion of Apoptosis:

eg: Follicular Lymphoma → t (14 : 18)

IgH ← ⊏ ⊐ → bcl 2

over expression of bcl 2

↓

anti apoptotic

↓

cancer

Sustained angiogenesis, metabolic alterations

00:46:10

Sustained Angiogenesis:

Pro Angiogenic factors   Anti Angiogenic factors

↓   ↓

VEGF   Vasculostatin

PDGF   Endostatin

FGF   Angiostatin

                                 Thrombospondin I

Active space

metabolic Alterations:
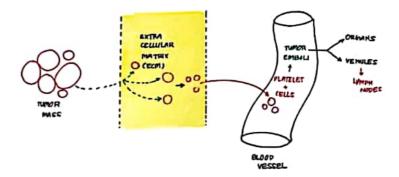
- Warburg Effect: Normal Cells in appropriate O_2 Concentration →
oxidative phosphorylation → ATP synthesis

Cancer cells — even when O_2 Concentration is normal they
undergo glycolysis — Glucose hunger

- This is utilized in PET-Scan

Invasion & metastasis   00:50:18

1) Tumor cells detach from each other by ↓ expression of E-Cadherin
2) Attach to ECM by Integrins —Combine with→ Laminin, Fibronectin
3) ECM degradation & Breakdown of Basement membrane by mmp's
   & Type iv Collagenase
             (matrix metalloproteinases) → mmp's (2,9*)
4) Cells enter blood vessels
5) Cells + Platelets → Tumor emboli ┬ Organs
                                    └ Via venules → Lymph Nodes

Active space

NEOPLASIA - BASIC CONCEPTS - III

Chemical carcinogenesis   00:00:14

Chemical		Cancer
1.	Polycyclic aromatic Hydrocarbons (PAH)	→ Bronchogenic Cancer
2.	Aflatoxin	→ Hepatocellular Cancer
3.	Arsenic	→ Skin Cancer
4.	Asbestos	→ Lung cancer (adenocarcinoma) Pleural Cancer (malignant mesothelioma)
5.	Polyvinyl Chloride (PVC)	→ Hepatic angiosarcoma
6.	Diethyl stilbestrol	→ Vaginal cancer
7.	Benzene	→ Leukemia
8.	β-Naphthylamine/Azo dyes	→ Bladder Cancer
9.	Cadmium	→ Prostrate cancer
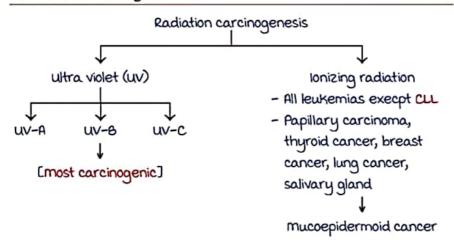
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Radiation carcinogenesis   00:03:41

Radiation carcinogenesis

Ultra violet (uv)

UV-A   UV-B   UV-C
         ↓
    [most carcinogenic]

Ionizing radiation
- All leukemias execpt CLL
- Papillary carcinoma, thyroid cancer, breast cancer, lung cancer, salivary gland
         ↓
  mucoepidermoid cancer
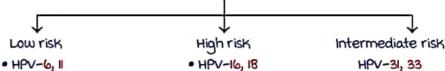
Microbial carcinogenesis   00:05:21

1. H. pylori   -   Gastric adenocarcinoma
               -   maltoma

a. HPV (Human Papilloma Virus)

Low risk	High risk	Intermediate risk
• HPV-6, 11	• HPV-16, 18	HPV-31, 33

• Condyloma acuminatum	• Cervical cancer
	  Anogenital cancer
	  Laryngeal cancer	

• Pathogenesis

  Has 2 proteins
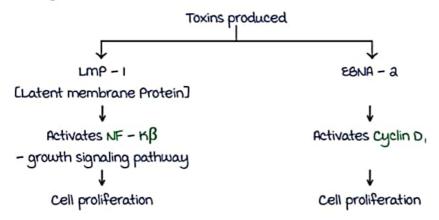
  i) E_6 + P53 → Inactivates P53 → carcinogenesis
  ii) E_7 + Rb → inactivates Rb → carcinogenesis

• microscopy

  i) Koilocytic changes
    – Cells with thick membrane
    – Resin like nucleus
    – Perinuclear halo/hoff

3. HBV (Hepatitis B virus) ⎫
                           ⎬ – Hepatocellular carcinoma
4. HCV (Hepatitis C virus ⎭

5. HTLV – II (Human T-cell leukemia virus) – T cell leukemia

6. HHV – 8 (Human Herpes Virus) – Kaposi's sarcoma

                                – 1° effusion lymphoma
                                – multicentric castleman disease

7. EBV (Ebstein Barr Virus)

   – Affects B-lymphocytes (mostly)
   – Receptor : CD – 21
   – Neoplastic lesions caused by EBV – i) Hodgkin's lymphoma
                                        ii) Non-hodgkin's lymphoma
                                        iii) Extra Nodal T-cell lymphoma
                                        iv) Nasopharyngeal carcinoma
                                        v) Burkitt's lymphoma
                                        vi) Post transplant
                                            lymphoproliferative
                                            disorders (PTLD)

Active space

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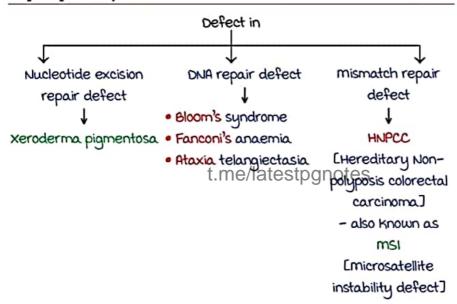
Non-neoplastic lesion – infectious mononucleosis

Pathogenesis

Toxins produced

LMP – 1
[Latent membrane Protein]
↓
Activates NF – KβB
– growth signaling pathway
↓
Cell proliferation

EBNA – 2
↓
Activates Cyclin D₁
↓
Cell proliferation

Repair pathway defects   00:14:43

Defect in

| Nucleotide excision repair defect | DNA repair defect | mismatch repair defect |

Xeroderma pigmentosa

DNA repair defect
↓
• Bloom's syndrome
• Fanconi's anaemia
• Ataxia telangiectasia

mismatch repair defect
↓
HNPCC
[Hereditary Non-polyposis colorectal carcinoma]
– also known as
MSI
[microsatellite instability defect]

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Paraneoplastic syndrome   00:17:32

Symptom complexes in cancer patients which cannot be explained by the local or indigenous spread of tumor

Syndrome	Tumor	Substance produced
1. SIADH (syndrome of Inappropriate ADH secretion)	Small cell carcinoma of lung	ADH
2. Cushing's Syndrome	Small cell carcinoma of lung	ACTH
3. Hypercalcemia	• Squamous cell carcinoma of lung • Carcinoma breast	Parathyroid Hormone related Peptide (PTHrp)

Active space

4. Polycythemia	• Renal cell carcinoma	Erythropoeitin
5. Hypoglycemia	• Ovarian carcinoma • Fibrosarcoma	Insulin and insulin like growth factor
6. migratory thrombophlebitis	• Carcinoma pancreas • Carcinoma colon	–
7. Hypertrophic pulmonary osteoarthropathy	• Small cell carcinoma of lung	–
8. myasthenia gravis	• Thymoma • Carcinoma lung	–
9. Acanthosis Nigricans	• Carcinoma stomach • Carcinoma colon	Epidermal growth factor

i) most common paraneoplastic syndrome → Hypercalcemia
ii) Tumor producing Paraneoplastic syndrome → Small cell carcinoma lung

Tumor markers   00:24:41

- Substance released by tumor into the blood
- Uses
  - Diagnosis
  - prognosis
  - Response to treatment
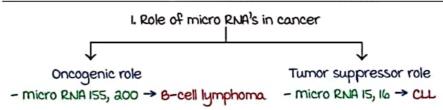
marker	Tumor
1. Prostate specific antigen (PSA) 2. Prostate acid phosphatase (PAP)	→ Prostate cancer
3. Alpha fetoprotein (AFP)	→ i) Hepatocellular carcinoma (HCC) ii) Non-seminomatous germ cell tumor (NSGCT) – Yolk sac tumor
4. β-hCG	→ i) Choriocarcinoma ii) Gestational trophoblastic disease
5. CA-125	→ Ovarian cancer

Active space
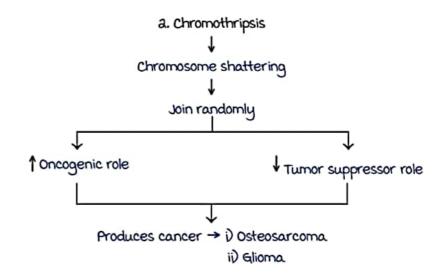
6. CA 19-9	→ i) Colonic cancer ii) Pancreatic cancer
7. CA-15-3	→ Breast cancer
8. Catecholamines	→ Pheochromocytoma
9. Immunoglobulins	→ multiple myeloma
10. Calcitonin	→ medullary carcinoma thyroid
11. Carcino embryonic antigen	→ i) Colon cancer ii) Pancreatic

Immunohistochemical markers   00:29:25
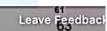
Cell of origin	marker
1. Epithelial origin	Cytokeratin
2. mesenchymal origin	Vimentin
3. Glial origin	Glial fibrillary acidic protein (GFAP)
4. Smooth muscle origin	Smooth muscle actin (SMA)
5. Skeletal muscle origin	Desmin, myogenin, myoD-1
6. Vascular origin	• VWF (von willebrand factor) • CD-31 • VEGF (vascular endothelial growth factor)
7. Neuroendocrine origin	– Synaptophysin – Chromogranin – Neuron specific enolase
8. GIST (Gastro Intestinal stromal Tumor)	• CD-117 (c-KIT) • DOG-1 • CD-34
9. malignant melanoma	– HMB-45 – S-100
10. malignant mesothelioma	• Calretinin • CK-5/6
11. Ewing's sarcoma	– CD-99 (MIC-2)
12. Hepatocellular carcinoma	• Hep par-1 • Arginase-3
13. Osteosarcoma	– Osteopontin – Osteonectin – Osteocalcin
14. Chondrosarcoma	S-100
15. Liposarcoma	S-100

Active space

Recent advances in neoplasia   00:36:00

I. Role of micro RNA's in cancer

Oncogenic role | Tumor suppressor role
- micro RNA 155, 200 → B-cell lymphoma | - micro RNA 15, 16 → CLL

a. Chromothripsis
↓
Chromosome shattering
↓
Join randomly

↑ Oncogenic role   ↓ Tumor suppressor role

Produces cancer → i) Osteosarcoma
                  ii) Glioma

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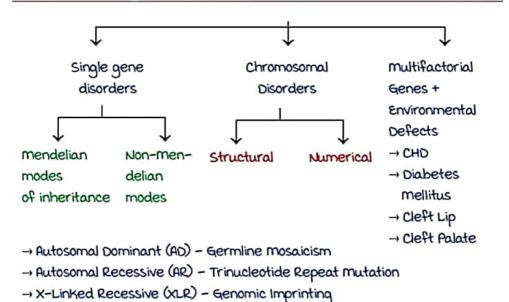
GENETICS – MENDELIAN MODES

Classification of genetic diseases   00:01:12

```
          ┌──────────────┬──────────────────┬──────────────────┐
          ↓              ↓                  ↓
     Single gene    Chromosomal       multifactorial
      disorders      Disorders        Genes +
          │              │            Environmental
    ┌─────┴─────┐   ┌────┴─────┐      Defects
    ↓           ↓   ↓          ↓      → CHD
mendelian   Non-men-  Structural  Numerical   → Diabetes
modes       delian                              mellitus
of inheritance  modes                         → Cleft Lip
                                              → Cleft Palate
```

→ Autosomal Dominant (AD) – Germline mosaicism

→ Autosomal Recessive (AR) – Trinucleotide Repeat mutation

→ X-Linked Recessive (XLR) – Genomic Imprinting

→ X-Linked Dominant (XLD) – mitochondrial inheritance

Mendelian modes of inheritance – autosomal dominant   00:04:51

- m = F

- Can also be expressed in Heterozygous state

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- At least one parent of index case is affected

- Adult onset

- Skip generations – Absent

- Due to defect in structural proteins

- 2 properties:

→ Incomplete penetrance

    - Eg: 100 people – defective NF1 gene

    - 80 people – show disease

    - Penetrance = 80%

Active space

→ Variable Expressivity

Eg: 4 people: have defective gene for NF-1, of the 4 people:

1 will have cafe Au lait spots

2 will have Neurofibromas

will have Lisch nodules

- Examples :-

→ Mnemonic: He has a very dominant Father

He → Huntington's Disease

Has → Hereditary Spherocytosis

A → Autosomal Polycystic Kidney Disease

Very → VWD, VHL

D → Dystrophia Myotonica

O → Osteogenesis imperfecta

m → marfan's Syndrome

I → Intermittent porphyria

N → NF-1

A → Achondroplasia

N → NF-2

T → Tuberous Sclerosis

Father → Familial Adenomatous polyposis,

Familial Hypercholestrolemia

AD – m.C mode of inheritance

Marfan syndrome   00:14:51

- Deficiency in FBN 1 gene (encodes for Fibrillin 1)
- Deficiency in FBN 2 gene (encodes for Fibrillin 2)

↓

Congenital Contractural Arachnodactyly

Clinical Presentations

→ Skeletal defects   → Tall stature
   (most characteristic feature)   → Hyper extensible joints (Thumb)
                              → Dolicocephalic Head

Active space

→ Ocular defects ⟶ Ectopia Lentis
⟶ Supero temporal dislocation of lens.

→ CVS defects ⟶ mitral valve Prolapse(also in Klinefelter's Disease)
⟶ Aortic dissection

MC cause of death – Aortic Dissection (CVS)

Diagnosis of marfan's Syndrome:

Revised Ghent's Criteria

→ Family History

→ Signs and symptoms

→ Fibrillin I gene mutation

Neurofibromatosis type I and II   00:20:44
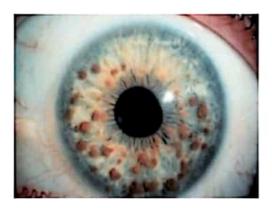
NF–I

- Gene on chromosome 17 – encodes for Neurofibromin
- a/k/a von Recklinghausen's Disease
- Patient can present with:
  1. Cafe-au-lait spots- (>6 spots)

2. Lisch nodules
   → Pigmented Iris Hamartomas

3. Neurofibromas

   meningiomas

   Pheochromocytoma

- Can be associated with Juvenile myelo monocytic Leukemia (JMML)

NF-2

- Gene on chromosome 22 – encodes for merlin
- Associated with Bilateral Acoustic Neuromas/Schwannomas

Ehler danlos syndrome (EDS)   00:24:47

- → AD
  → AR → Type 6
        → Type 7
- m.c type of EDS → Type 3
- Least common type of EDS → Type 7
- most dangerous type of EDS → Type 4 (Vascular)
- Types
  → Types I & II   Diaphragmatic Hernia
     (classical)   mitral Valve prolapse
  → Type 3 EDS   : → Loose Skin (Rubberman syndrome)
     (Hypermobility) : → Thin skin (Cigarette paper skin)
  → Type 4 EDS   : Aorta may rupture
     (vascular)
  → Type 6 EDS   : Defect in Lysyl Hydroxylase enzyme
     [Kyphoscoliosis (AR)]
     Type 7 EDS : → 7 a, b : Arthrochalasia → joint, bone defects
                  → 7 c: Dermatosparaxis → severe skin fragility
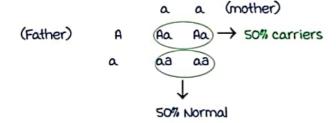
Active space

Autosomal recessive disorders   00:29:36

- m = F
- Only expressed in homozygous state
- Compete penetrance
- Young/early onset
- Skip generations can be seen
- Usually due to Enzyme deficiency
- If :

Father → Carrier (Aa)

mother → Normal (aa)


```
                    a     a    (mother)
   (Father)    A    Aa    Aa  → 50% carriers
               a    aa    aa
                         ↓
                    50% Normal
```

→ In some cases:

Father → Carrier

mother → Normal

Child → can be affected → uniparental Disomy

(Both alleles are from a single parent)

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Examples :

A → Alkaptonuria, Ataxia, Albinism

B → Beta thalassemia, sickle cell anemia

C → Cystic Fibrosis, Congenital Adrenal Hyperplasia

D → Deafness

E → Emphysema (α_1 Antitrypsin deficiency)

F → Friedreich's Ataxia

G → Glycogen storage disease, Galactosemia

H → Haemachromatosis, Homocystinuria

I → Inborn errors of metabolism

Active space

Lysosomal storage disorders

00:37:08

- m.c → Gaucher's Disease
- All are AR except ⌐→ Fabry's Disease
                    └→ Hunter's Disease
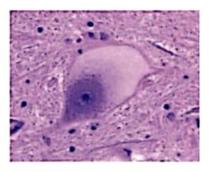
Tay sachs Disease
- mnemonic : TAY SACHS
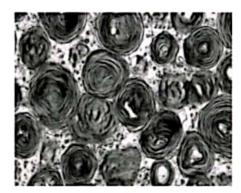
T → Tay Sachs

A → Ashkenazi Jews

Y → Young

S → Spot (Cherry red Spot in macula)

A → AR

C → CNS defects (neurons ballooned / Vacuolated)

H → Hexosaminidase α Sub unit defect ↑ GM 2 Ganglioside

S → Symptoms (motor neuronal functions, mental retardation)

Warning : Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with marrow Edition 4 videos.   t.me/latestpgnotes

- Histopathology :
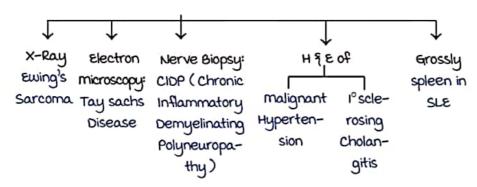
→ Neuron :
- Ballooned
- Vacuolation
  (distended
  with Lysosomes)

Electron microscopy :
→ onion skin Appearance

Onion Skin Appearances

X-Ray Ewing's Sarcoma	Electron microscopy: Tay sachs Disease	Nerve Biopsy: CIDP (Chronic Inflammatory Demyelinating Polyneuropathy)	H & E of		Grossly spleen in SLE
			malignant Hypertension	I° sclerosing Cholangitis	
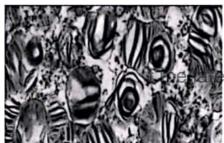
Niemann Pick's Disease

- Defect in Sphingomyelinase

  ↓

  Accumulation of Sphingomyelin

- On Electron microscopy:

Zebra Bodies

- Clinically divided into types :
→ Type A : Neuronal involvement ☒
    Severe, early mortality
→ Type B : Neuronal involvement ⊖
    Better prognosis
→ Type C : most Common
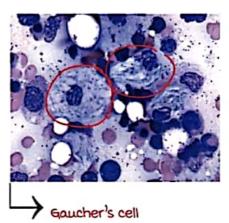
Gaucher's Disease

- Deficiency of Glucocerebrosidase
    Accumulation of Glucocerebroside

- Bone marrow Aspirate : Gaucher's Cell
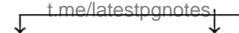
→ Gaucher's cell
- Wrinkled /crumpled tissue paper Appearance
- PAS +
  Oil red O +
  Perl's +

→ Pseudo Gaucher's cell ☒ seen in CML
            − Perl's stain Negative

- Clinically

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Non −Neuronopathic	Neuronopathic	Intermediate
→ Adulthood	→ Infants	
→ mc	→ less common	
→ Bone involvement, Pathological fractures, Hepatosplenomegaly	→ more severe → CNS involvement	

Lysosomal Storage disorders: Mucopolysaccharidoses   00:50:58

- Defect in enzymes which degrade glycosaminoglycans
- Accumulation of: Dermatan sulphate
                   Chondroitin sulphate
                   Heparan sulphate
- Clinical Presentation: Hepatosplenomegaly
                     Coarse facial features
                     mental retardation
                     Corneal clouding

Active space

- a Categories ⟶ Hunter Disease (XLR)
  ⟶ Hunter Disease (AR)

X-linked recessive disorders (XLR)   00:52:27

- M>>>F
- Females are usually carriers
- Females can be affected when there is random X chromosome inactivation during Lyon's Hypothesis
- Examples:

mnemonic : Lady Hardinge college girls don't care about foolish words

Lady ⟶ Lesch Nyhan Syndrome

Hardinge ⟶ Hemophilia A and B, Hunter's disease

College ⟶ Colour Blindness

Girls ⟶ G6PD deficiency.

Don't ⟶ Duchenne muscular Dystrophy.

Care ⟶ Chronic Granulomatous Disease

About ⟶ Agammaglobulinemia

Foolish ⟶ Fabry's disease, Fragile X Syndrome

Words ⟶ Wiscott Aldrich Syndrome

X-linked dominant disorders

- mother : can give the disease to both sons and daughters
- Father : affects only daughters, not sons
- Examples :
  R ⟶ Rett's Syndrome
  A ⟶ Alport Syndrome
  V ⟶ Vit D resistant rickets
  I ⟶ Incontinentia pigmenti

Active space

- Homozygous Dominant is incompatible with life .
- In dominant disorders → Genotype is Heterozygous

Active space

GENETICS-NON MENDELIAN MODES

Mitochondrial inheritance   00:00:33
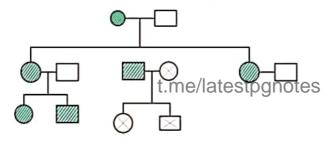
→ Exclusively maternally inherited

    Normal sperm   +   Normal ova
       mt-DNA   mt-DNA

             Fuse

→ Ova eliminates all sperm mitochondrial DNA bu

   Ubiquitin proteasome pathway

   Zygote DNA contains only maternal mitochondrial DNA

→ mother transmits disease , to all offsprings.

   Father to none   ⬤ Diseased

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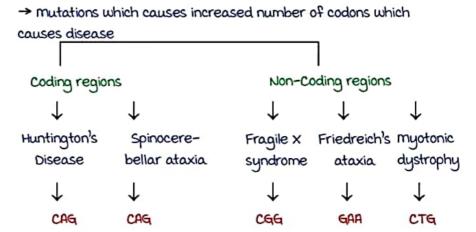
→ These diseases usually affects- Brain

                   - Eye

                   - skeletal muscle

→ Heteroplasmy: presence of normal + mutant mitochondrial DNA in

                same person.

→ Examples:

① Kearns Sayre Syndrome

② Leigh syndrome, Leber Hereditary Optic neuropathy

③ MELAS- mitochondrial Encephalopathy, Lactic acidosis
     and Stroke like episodes m/c mitochondrial disorder.

④ NARP syndrome

⑤ CPEO- chronic progressive external opthalmoplegia

         mc mitochondrial myopathy

⑥ Pearson's Syndrome

Active space

Trinucleotide repeat mutations   00:08:28

→ mutations which causes increased number of codons which causes disease

Coding regions
↓   ↓
Huntington's   Spinocere-
Disease   bellar ataxia
↓   ↓
CAG   CAG

Non-Coding regions
↓   ↓   ↓
Fragile X   Friedreich's   myotonic
syndrome   ataxia   dystrophy
↓   ↓   ↓
CGG   GAA   CTG

→ These diseases mostly involve cytosine and guanine nucleotides

Fragile X Syndrome:
→ Due to mutation in FMR I gene
                    ↓
              ↑ CGG repeats
Normal → 5-40 CGG Repeats
Premutation → 55-200 CGG Repeats
Full mutation → 200-4000 CGG Repeats
→ Anticipation/Sherman's paradox
    - severity of disease increases with each successive generation
    - increase CGG repeats with each generation
→ Called fragile X Syndrome because
                    ↓
    when cells are cultured in Folate deficient media
                    ↓
    Constriction is seen in " X Chromosome"
                    ↓
    Appears as X chromosome is broken.
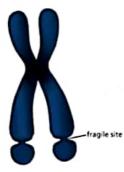
Normal X chromosome   Fragile-X chromosome
                                    fragile site

Active space

→ Clinically :
1) 2ⁿᵈ mc genetic cause of mental retardation (1ˢᵗ mc
    cause-Down's syndrome)
2) Large head, large everted ears
3) Large jaw/mandible
4) Large testis (macroorchidism)
→ most distinctive feature.

Fragile X tremor syndrome:

- gene FMR I
- Gain of function mutation
        ↓
    intentional tremors

Gonadal mosaicism   00:18:51

→ Type of Autosomal dominant disorder
→ If both parents are normal but child is affected
            ↓
        gonadal mosaicism
    Normal sperm + Normal ova
            ↓
        zygote
         ↓ post zygotic mutation.
    Present only in gametes not in somatic cells
→ Examples:
① Tuberous sclerosis
② Osteogenesis imperfecta

Genomic imprinting   00:22:06
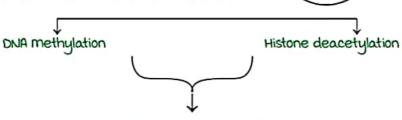
- Gene Silencing/Inactivation
- either paternal/maternal allele is inactivated.
        ↓
    Only one allele is functional
- Normal phenomenon
Epigenetics
    Heritable modifications in DNA/ histones
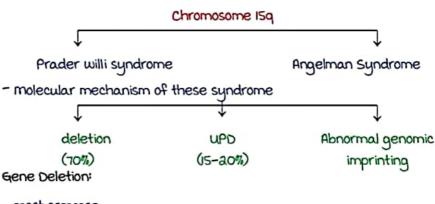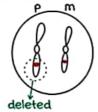
DNA methylation   Histone deacetylation

        Decreased expression of genes.

Active space

Prader willi syndrome   00:26:46

Chromosome 15q

Prader willi syndrome   Angelman Syndrome

- molecular mechanism of these syndrome

deletion   UPD   Abnormal genomic
(70%)   (15-20%)   imprinting

Gene Deletion:

- most common

deleted

maternal allele → only functional
is silenced   allele is paternal
↓
Paternal deletion and maternal silencing
↓
Prader willi syndrome
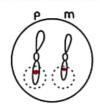
→ Clinical features:
 - short stature
 - hypotonia
 - hypogonadism
 - hyperphagia → obesity
          ↓
Due to increase Ghrelin hormone
 - mental retardation
→ Prader willi is due to loss of function mutation in snorp gene

Angelman Syndrome   00:31:37

→ paternal gene is silenced
→ only maternal gene was functional

maternal deletion + paternal silencing
↓
Angelman syndrome
or
Happy Puppet Syndrome
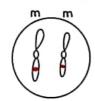
→ Clinical features:
① Inappropriate laughter
② Ataxia
③ Seizures
④ Hypotonia
⑤ mental retardation

Active space

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Uniparental disomy   00:34:12
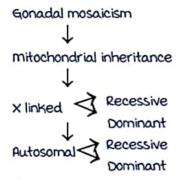
→ If both alleles come from same parent.

m   m

→ paternal deletion/maternal disomy
Prader willi

→ Paternal disomy → Angelman syndrome

→ Angelman is due to defect in ubiquitin ligase (UBE3A)

Pedigree analysis   00:37:40

Gonadal mosaicism
↓
mitochondrial inheritance
↓
X linked ⟨ Recessive
           Dominant
↓
Autosomal ⟨ Recessive
            Dominant
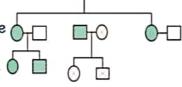
Gonadal mosaicism:

- autosomal dominant
- Both parents are normal
- Any number of children are affected

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mitochondrial Inheritance:

- Affected mother transmits disease
  to all kids
- Affected father does not transmit
  disease to kids
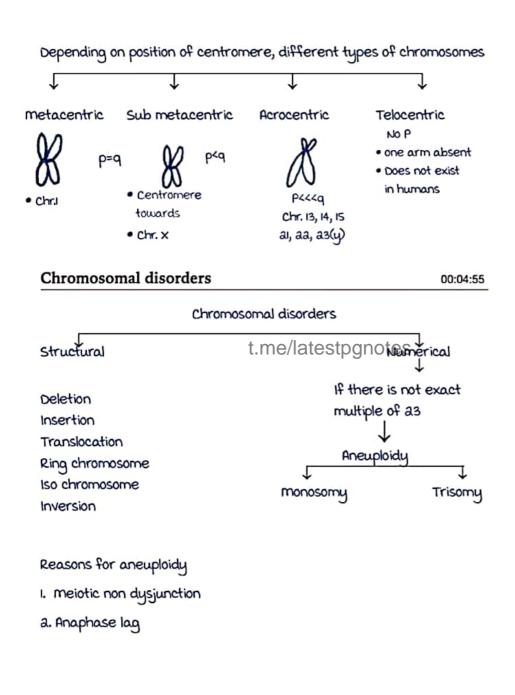
X-Linked recessive dominant:

→ m>>>F

→ Females are usually carriers

→ If skip generation ——→ present-recessive.
                       ↘ Absent-dominant.

→ In X-linked dominant disorder:
- mother transmits disease to both son and daughter
- Father transmits disease only to daughter

Autosomal Dominant/Recessive:

→ m = F

→ skip generations ——→ Present - recessive
                      ↘ Absent - dominant

Active space

GENETICS - CHROMOSOMAL DISORDERS

Depending on position of centromere, different types of chromosomes

metacentric	Sub metacentric	Acrocentric	Telocentric

metacentric
$p=q$
• Chr.1

Sub metacentric
$p<q$
• Centromere towards
• Chr. X

Acrocentric
$p<<<q$
Chr. 13, 14, 15
21, 22, 23(y)

Telocentric
No P
• one arm absent
• Does not exist in humans

Chromosomal disorders   00:04:55

Chromosomal disorders

Structural   t.me/latestpgnotes   Numerical

Deletion
Insertion
Translocation
Ring chromosome
Iso chromosome
Inversion

If there is not exact multiple of 23

↓

Aneuploidy

monosomy   Trisomy

Reasons for aneuploidy

1. meiotic non dysjunction

2. Anaphase lag

Active space

Structural abnormalities   00:08:13

A. Deletion   portion of chromosome deleted

B. Insertion   portion of chromosome inserted

C. Ring chr.   Break at both ends

                 fusion of damaged ends

                 can be seen in Turner syndrome

D. Inversion   −A   A−B

                              −B   B−A

                              −C

Paracentric   pericentric
(If same side of   (opposite sides)
centromere)

E. Translocation −   Exchange of material b/w two chromosomes.

Balanced   Robertsonian
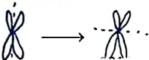
                 Translocation between a acrocentric
                 chromosomes.
                 Chr. 13, 14, 15, 21, 22, Y ↓
                 One very short arm and one very long arm
                 t(14: 21) − Down's syndrome

E. Isochromosome

                  two short/ Two long arms

mc Isochromosome ixy

mc Isochromosome Cancer i17q

mc Isochromosome testicular tumor i12p

Active space

Down's syndrome   00:16:25

Trisomy 21

   mc chromosomal disorder

   mc genetic cause of mental retardation

Pathogenesis → meiotic non dysjunction (95%)

                    occurs in oogenesis

              → Translocation Robertsonian (4%)

                    t (14; 21)

              → mosaics (1%)

Screening   (0 – 35 yrs, but routinely done in all women)

Triple test – AFP

              βhcG

              unconjugated estradiol

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Quadruple test   Triple+ inhibin

Clinical features   00:20:43

1. mental retardation
2. Face → Flat facial profile
       → Oblique fissure
       → Prominent epicanthal folds
       → Flat occiput
       → Flat nasal bridge
       ∴ called mongoloid idiocy
3. Eyes – Brush field spots
4. Palm – Single palmar crease
              (Simian crease)

          – clinodactyly

5. Foot – Sandle gap/ saddle toe
          (↑ gap between first two toes)

Upslanting palpebral fissures
Low-set, small folded ears
Short neck
Epicanthal fold
Flattened nasal bridge
Brushfield spots
Small, typically white, spots, arranged in a ring
Upper eyelid skin fold covers the inner corner of the eye

Active space

Complications of down's syndrome 24:20

I. Acute leukemia

    MC leukemia– ALL

    MC leukemia in children < 3yrs– AML

    MC type of AML – AML m7

2. Cardiovascular defect

    MC Cardiovascular defect– Endocardial cushion defect

                                      VSD

3. GIT
    → Annular pancreas
    → Duodenal atresia
    → Hirschsprung disease

4. Endocrine – Hypothyroidism

5. CNS   premature Alzheimer's disease

            (∴ gene for Alzheimer's disease is on chr. 21)
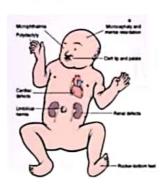
Other trisomies 00:27:40
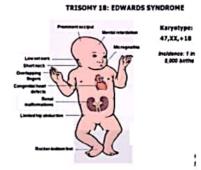
Trisomy 13	Trisomy 18
PATAU	EDWARD

mental retardation
← CVS defect →
Rocker bottom feet
prominent occiput

microcephaly	micrognathia
micro ophthalmia	short neck
umbilical hernia	Renal malformation
polydactyly	Limited hip abduction
left Lip & palate	overlapping fingers

TRISOMY 18: EDWARDS SYNDROME

Karyotype: 47,XX,+18

Incidence: 1 in 8,000 births

meiotic non dysjunction occurs On meiosis – I
except in Edward's syndrome (It occurs in meiosis II)

Active space

del 22q 11.2

C Cleft Lip/ Palate
A Abnormal facies
T Thymic hypoplasia
C cardiac defect
H Hypocalcemia
22 – del 22q11.2

*Defect in development of 3rd & 4th pharyngeal
pouch
∴ causes thymic & Parathyroid hypoplasia

aka   DiGeorge syndrome
             Velo cardio facial defects
                  ↓
Trisomy 22 (cat – eye syndrome)

• Multiple colobomas in the eye.

Cat cry syndrome (del 5p)

• cat like cry
• Behavioral abnormalities
• Developmental delay

Sex chromosomal disorders   00:34:52

Lyon's hypothesis

1) only one of the X-Chromosomes is genetically active

2) Other X, of either paternal or maternal origin
   becomes inactive (occurs randomly)

3) Inactivated X chromosme – Barr Body
   Sample   : buccal mucosa
   Shape   : drumstick appearance

Clinical applications
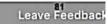
Normal male	XY	→	'o' BB
Normal Female	XX	→	'1' BB
Turner's	XO	→	'o' BB
Klinefelter	XXY	→	'1' BB
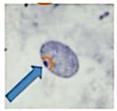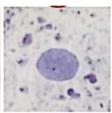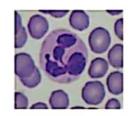
No. of barr body = No. of X chromosme –1

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Active space

* 21 % genes on Xp and 3% genes on Xq escape inactivation

Klinefelter's syndrome   00:40:35

MC cause of male hypogonadism

Pathology   : xxy → xxxy → xxxY
                  more the no of x chr, more is the mental retardation

meiotic non dysjunction
(can occur in paternal & maternal gamete)
Syndromes associated with advanced maternal age.
    – Down's Syndrome
    – XXX syndromed

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Syndromes associated with advanced paternal age
    – marfan syndrome
    – Osteogenesis imperfecta
    – Achondroplasia

Syndromes associated with both advanced maternal and paternal
    – Klinefelter

Clinical features
1) Tall stature
2) Eunuchoid body
   habitus
3) Long extremities
4) Reduced 2°
   sexual characteristics
5) Gynecomastia
6) frontal baldness
   absent

Klinefelter syndrome

Frontal Baldness absent
Tendency to grow fewer chest hairs
Breast development
Female-type pubic hair pattern
Small testicular size
Poor beard growth
Narrow shoulders
Wide hips
Long legs

- **Lower IQ than sibs**

- **Tall stature**

- **Poor muscle tone**

- **Reduced secondary sexual characteristics**

- **Gynaecomastia (male breasts)**

- **Small testes/infertility**

7) poor muscle tone

8) "Testicular atrophy"

      ↓

    Infertility

Biopsy: Atrophy of seminiferous lobules

        Hyalinisation of lobules

        Leydig cell hyperplasia

Hormonal changes ↑ FSH   ↑ LH   ↓ Testosterone

CVS changes – MVP

MC Cancer · Breast Cancer

MC germ cell tumor– Extragonadal GCT

             (Teratoma)

Turner's syndrome   49: 51

MCC– Female hypogonadism

monosomy x (xo)

Pathology   ⤷ Deletion of x chr.

           ⤷ Ring chr.
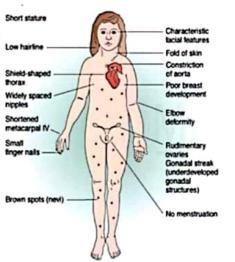
           ⤷ ISO chr.

Only monosomy compatible with life

mc monosomy – monosomy 16

Clinical features   00: 51: 45

* Webbed neck – lymphedema

  Elbow deformity – cubitus valgus

  ovaries – streaked ovaries

Short stature
Characteristic facial features
Low hairline
Fold of skin
Constriction of aorta
Shield-shaped thorax
Poor breast development
Widely spaced nipples
Elbow deformity
Shortened metacarpal IV
Small finger nails
Rudimentary ovaries
Gonadal streak (underdeveloped gonadal structures)
Brown spots (nevi)
No menstruation

Active space

mcc of primary amenorrhoea - Turner's

CVS abnormalities

- mc CVS defect bicuspid aortic valve
- mc cause of death preductal co-arcation of aorta

C - Cardiac abnormalities, cubitus valgus, cystic hygroma
L - Lymphedema
O - Streaked Ovaries
W - Webbed neck
N - Normal Intelligence, Nipples widely spaced
S - Short stature, short 4th metacarpal

- ↑ risk of developing gonadoblastoma

Noonan's syndrome

• Clinical features of Turner's
• Normal Karyotype
• Mutation in chromosome 12

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Karyotyping   00: 58: 05

• Study of chromosomes
• Karyogram: Arrangement of chromosomes in descending order of
          length followed by sex chromosomes.

• uses- structural & numerical abnormalities of chromosome
• Sample
    1. Amniotic Fluid
    2. Chronic villi sampling
    3. Skin fibroblasts
    4. Peripheral blood lymphocytes

Active space
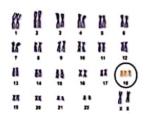
- Arrest the cell in metaphase
  (using Colchicine)

  Staining (banding)
  - mc. giemsa banding
  - Q- banding (quinatrine)

- Using light microscope, resolution required for Karyotyping

Turner's syndrome
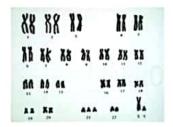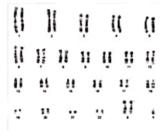
Edward's syndrome
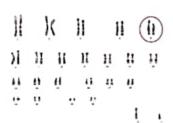
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Down's syndrome

Klinefelter's syndrome

Cri- du- chat syndrome
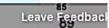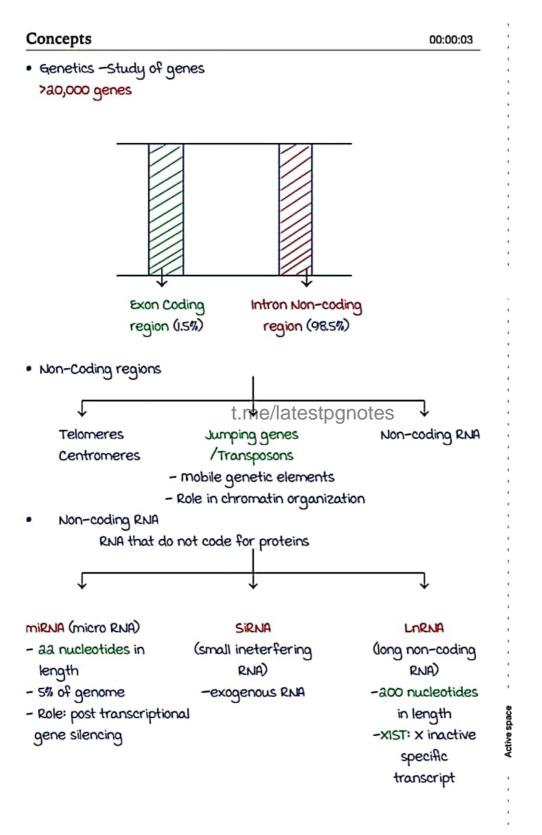
Active space
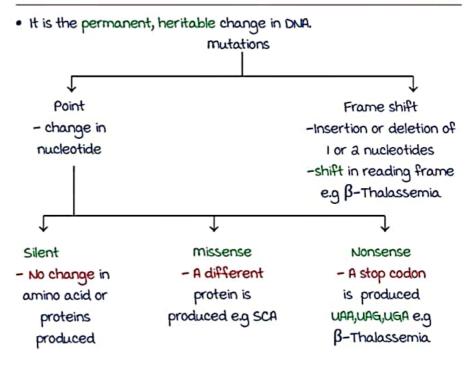
GENETICS – CONCEPTS AND DIAGNOSTICS

Concepts   00:00:03

- Genetics –Study of genes
  >20,000 genes

Exon Coding region (1.5%)   Intron Non-coding region (98.5%)

- Non-Coding regions

```
              ┌──────────────┼──────────────┐
              ↓              ↓               ↓
        Telomeres      Jumping genes    Non-coding RNA
        Centromeres    /Transposons
                   - mobile genetic elements
                   - Role in chromatin organization
```

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- Non-coding RNA
  RNA that do not code for proteins

```
              ┌──────────────┼──────────────┐
              ↓              ↓               ↓
```

miRNA (micro RNA)	SiRNA	LnRNA
- 22 nucleotides in length	(small ineterfering RNA)	(long non-coding RNA)
- 5% of genome	—exogenous RNA	-200 nucleotides in length
- Role: post transcriptional gene silencing		-XIST: X inactive specific transcript

Active space

Mutations   00:06:03

- It is the permanent, heritable change in DNA.

```
                    mutations
                        |
         ┌──────────────┴──────────────┐
         ↓                             ↓
      Point                       Frame shift
   – change in                -Insertion or deletion of
   nucleotide                    1 or 2 nucleotides
         |                      -shift in reading frame
         |                       e.g β-Thalassemia
    ┌────┼────────────┐
    ↓              ↓              ↓
 Silent         missense       Nonsense
- No change in  - A different  - A stop codon
 amino acid or    protein is    is produced
  proteins      produced e.g SCA  UAA,UAG,UGA e.g
  produced                        β-Thalassemia
```

Epigenetics   00:12:36

- Definition: Hereditary modifications in DNA or histones at a
  functional level

```
              Caused due to:
                    |
         ┌──────────┴──────────┐
         ↓                     ↓
   DNA methylation       Histone deacetylation
   (more common)
         |                     |
         └──────────┬──────────┘
                    ↓
             ↓ Expression of genes
```

- Lab Diagnosis of Epigenetics

A	B	C	D	E	F
Analysis	Bisulphite sequencing	chromatin immuno precipitation assay	DAM id DNA Adenine methyl transferase identification	Epigenetics	FISH

Definitons: 00:17:11

- Pleiotropy : Single gene has multiple end effects.
- Codominance: a dominant alleles expressing together
    e.g: ABO Blood grouping, HLA Typing

- Incomplete penetrance : The genetic defect does not penetrate
                the gene completely
- Variable expressivity : same genetic defect produces different
                clinical features in different patients
- Genetic polymorphism : a individuals have 99.5% common genes
        Differ only in 0.5% of genes
                    ↓
            genetic polymorphism

- Type of genetic polymorphism:

```
                    |
        ┌───────────┴───────────┐
        ↓                       ↓
```

SNP   **CNV**
Single nucleotide   Copy number
Polymorphism   variation
- variation in single nucleo-   - variations in large
tide/1000 base pairs   stretches of genome
- 1% occur in coding regions   from 1000 base pairs
                                    to a million base
                                    pairs
                                    - 50 % occur in coding
                                    regions

DIAGNOSIS OF GENETIC DISORDERS

I. Blotting techniques: ┌→ Northern Blot → RNA
    North – Roti   ├→ Southern Blot → DNA
    South – dosa   └→ Western Blot → Proteins
    West – pizza
a. PCR:
    - used to identify small DNA sequences
    - Types:
    • Sanger sequencing: Gold standard for sequencing
    • RT- PCR : Real time PCR
            e.g: t (9:22) in CML
    • Pyrosequencing: used to identify cancer cells contaminated by
                other cells
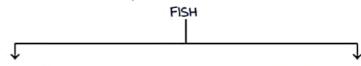
    • Amplicon length analysis: to identify trinucleotide repeat mutations.

Active space

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- Single base primer extension: to identify known mutations
  e.g BRAFV600
- Restriction fragment length : to identify unknown nucleotide position
- Pitfalls: cannot identify ⟶ Complex rearrangements
  ⟶ Duplications
  ⟶ Deletions

3. Hybridization:
- FISH − Fluroscence in situ hybridization
  - used when target gene is known:
    - Aneuploidies, translocations, deletions
    - Her 2 neu amplification in Breast Cancer

FISH
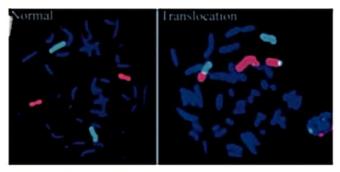
Chromosomal Painting,   Spectral Karyotyping

- Applications of FISH = Translocations in pathology
  t (9:22) ⟶ CML
  t (8:14) ⟶ Burkitt's Lymphoma
  t (11:14) ⟶ mantle cell Lymphoma
  t (14:18) ⟶ Follicular cell Lymphoma
  t (11:18) ⟶ marginal zone Lymphoma
  t (8:21) ⟶ AML-m2
  t (15:17) ⟶ AML-m3
  t (11:22) ⟶ Ewing's sarcoma

4. MLPA− Multiplex Ligation Probe Analysis
  - PCR + FISH: can detect deletions and duplications of any size
5. CGH − Comparative genomic hybridization
  - visualize unknown genetic loci

Active space
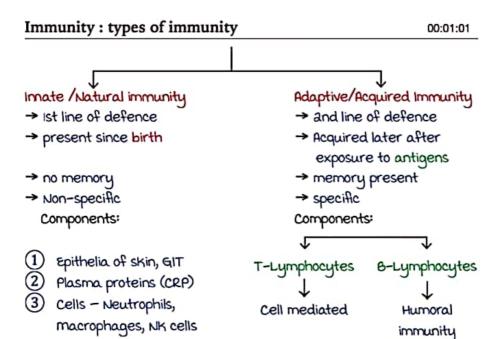
GEEN 00:39:25

- Genome Editing with Engineered Nucleases
- It is a genetic engineering technique in which DNA can be inserted, deleted or replaced in the human genome by using molecular scissors (engineered nucleases)

- molecular scissors
  1. Zn- finger nuclear scissor
  2. meganuclease
  3. TALEN – Transcription activator-like effector nuclease
  4. CRISPR/ CAS 9
     Clustered Regularly Interspersed Short Palindromic Repeats

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Active space

IMMUNITY - TYPES OF IMMUNE CELLS

Immunity : types of immunity   00:01:01

Inate /Natural immunity
→ 1st line of defence
→ present since birth

→ no memory
→ Non-specific
   Components:

① Epithelia of skin, GIT
② Plasma proteins (CRP)
③ Cells – Neutrophils,
   macrophages, NK cells

Adaptive/Acquired Immunity
→ 2nd line of defence
→ Acquired later after
   exposure to antigens
→ memory present
→ specific
   Components:

   T-Lymphocytes   B-Lymphocytes
        ↓   ↓
   Cell mediated   Humoral
                        immunity

Pattern recognition receptors:

→   Component of innate immunity
→   Receptors on cells which recognizes specific pattern on the
    bacteria or viruses.
→   Location:
-   Plasma membrane
-   Cytoplasm
-   Endosomal vesicle

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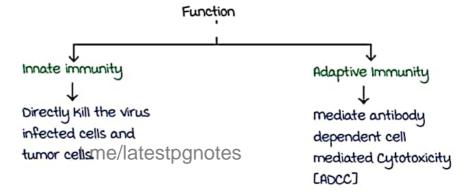
Cellular receptors   00:06:18

1) TLR – Toll like receptor
→ present on plasma membrane
→ 11 TLR's have been discovered
→ They recognize – gram +ve,
   gram –ve bacteria
2) C – LECTIN receptors.
→ present on plasma membrane
→ recognize fungal glycans

        TLR   CLR

        Cell

Active space

3) NOD like receptor

N → Necrotic debris - Uric acid in gout

O → Ion disturbances — K+ ions

D → Diabetes mellitus

→   Present on cytoplasm

4) RIG like receptors:

→ present on cytoplasm

→ recognize specific pattern on viruses
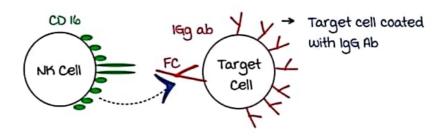
Natural killer cells – NK cell   00:10:10

→ Constitute 5-10% of circulating lymphocytes

→ These are non-B, non – T cells.

→ No BCR, no TCR

→ Not MHC restricted

<div align="center">Function</div>

Innate immunity
↓
Directly Kill the virus
infected cells and
tumor cells

Adaptive Immunity
↓
mediate antibody
dependent cell
mediated Cytotoxicity
[ADCC]

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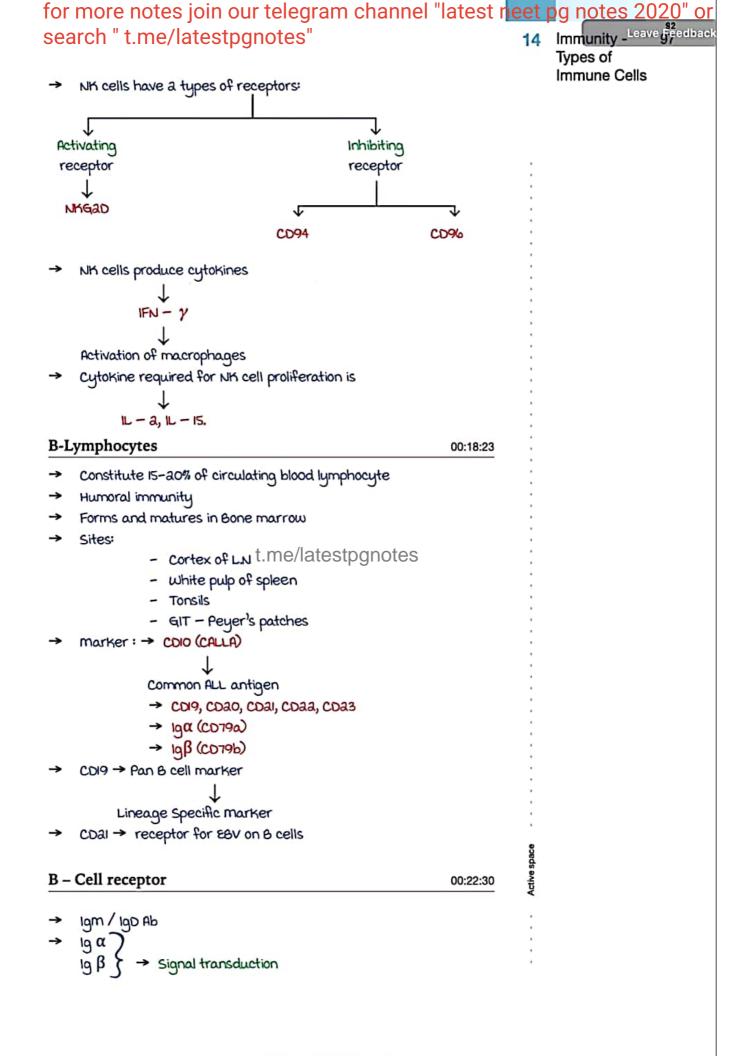
→ marker of NK cells:

① CD 16 – receptor for Fc fragment of IgG

② CD 56 (role not known)

CD 16

Igg ab

→ Target cell coated
  with IgG Ab

NK Cell   FC   Target
                 Cell

- CD 16 fits into Fc portion of IgG Ab

- NK cell release perforins and granzymes
   ↓
   Kill target cell
   ↓
   "Perforin granzyme mechanism"

Active space

→ NK cells have a types of receptors:

Activating receptor
→ NKG2D

Inhibiting receptor
CD94   CD96

→ NK cells produce cytokines
↓
IFN − γ
↓
Activation of macrophages

→ Cytokine required for NK cell proliferation is
↓
IL − 2, IL − 15.

B-Lymphocytes   00:18:23

→ Constitute 15−20% of circulating blood lymphocyte
→ Humoral immunity
→ Forms and matures in Bone marrow
→ Sites:
  - Cortex of LN t.me/latestpgnotes
  - White pulp of spleen
  - Tonsils
  - GIT − Peyer's patches

→ marker : → CD10 (CALLA)
↓
Common ALL antigen
→ CD19, CD20, CD21, CD22, CD23
→ Igα (CD79a)
→ Igβ (CD79b)

→ CD19 → Pan B cell marker
↓
Lineage Specific marker

→ CD21 → receptor for EBV on B cells

B – Cell receptor   00:22:30

→ IgM / IgD Ab
→ Ig α ⎱
  Ig β ⎰ → Signal transduction

Active space

→ CD40
   ↓
CD40 of B cell — interacts with CD 40 L of Tcell.
- Helps in interaction of B lymphocytes with T lymphocytes

           CD 40   CD 40 L

        B Cell   T Cell

Function:

              B Lymphocytes
                   ↓
              Plasma cells

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  IgG   IgA   IgM   IgD   IgE
   ↓   ↓   ↓   ↓
Crosses   mucosal   highest   released in
placenta   Secretion   molecular   Type I
                          weight   hypersensitivity
                            ↓   reactions
                         Pentamer

Antibody production by B cell.

T cell independent   T cell dependent
pathway   pathway
        ↓
Antigen is a lipopolysaccharide
        ↓
B cell produce plasma cell
        ↓
       IgM
→ No help of T cell is taken.

Active space

T – Cell dependent pathway   00:29:09

→   Proteinaceous antigen
$$\downarrow$$

B lymphocyte will combine →   Helper T Cell

● CD40   ● CD40L

(B cell)   (T cell)

IL – 4   IgM
IFN – γ IgD
$\downarrow$ $\downarrow$

IgG, IgA, IgE ← class switching

T – Lymphocytes   00:33:00

→   Constitute 60–70% of circulating blood lymphocytes
→   Formed in bone marrow
→   Mature in thymus
→   Help in cell mediated immunity
→   Sites:

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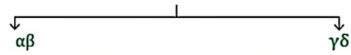
①   Paracortex of lymphnode
②   PALS (Periarteriolar lymphoid sheath of spleen)
③   Intra epithelial lymphocytes

markers:
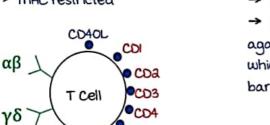
CD1, CD2, CD3, CD4, CD5, CD7, CD8
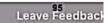
→ CD3 → Pan T cell marker
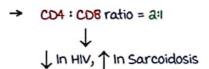
αβ	γδ
→ Present on 95% of T cells	→ Present on 5% of T cells
→ MHC restricted	→ Not MHC restricted
	→ Provides protection against the microbes which enter Through the barriers

CD40L
● CD1
αβ ⌐ (T Cell) ● CD2
        ● CD3
γδ ⌐   ● CD4
    ● CD5
CD7

Active space

→ CD4 : CD8 ratio = 2:1
↓
↓ In HIV, ↑ In Sarcoidosis

Helper T cells and cytotoxic T cells   00:39:45

Helper T cells	Cytotoxic T cells
① CD4+ T cells	① CD8+ T cells
② MHC II restricted	② MHC I restricted
③ master regulators of immune system – Ist line of defence	③ 2nd line of defence

Functions:

→ Helps B cells to produce antibodies	→ Helps to kill the cells by perforin granzyme mechanism.
→ Helps macrophages to destroy microbes	

Types of helper T cells: 00:42:26

TH1   TH2   TH17

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TH1 → IFNγ → Signature cytokine

- Helps in the production of
  IgG Ab

- Activates the complement by classical pathway
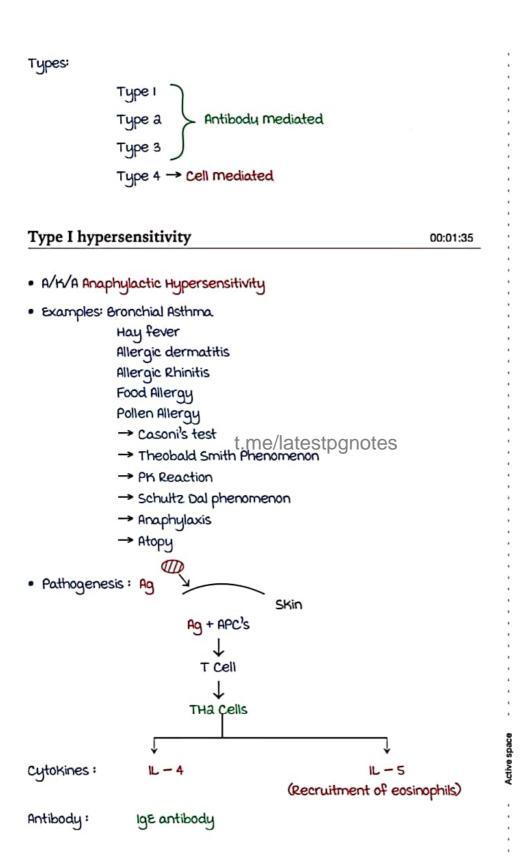
→ Provides host defence against Intra cellular microbes

Active space

TH2

IL-4
→ Signature
   cytokine
→ Stimulate B cell
   producing IgE ab
→ Activates
   macrophages by
   alternate pathway
→   Help against Helminthic parasites

IL-5
→ IgA ab
→ Activation
   of most cells.
→ Activation of
   eosinophils

IL-13
→ Activates
   macrophages by
   alternate pathway

TH17

IL-17   IL-22

→ Function:

-   Recruitment of neutrophils and macrophages
-   Host defence against extracellular microbes

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Active space

HYPERSENSITIVITY REACTIONS

Types:

Type I ⎫
Type 2 ⎬ Antibody mediated
Type 3 ⎭
Type 4 → Cell mediated

Type I hypersensitivity   00:01:35

- A/K/A Anaphylactic Hypersensitivity
- Examples: Bronchial Asthma
  Hay fever
  Allergic dermatitis
  Allergic Rhinitis
  Food Allergy
  Pollen Allergy
  → Casoni's test
  → Theobald Smith Phenomenon
  → PK Reaction
  → Schultz Dal phenomenon
  → Anaphylaxis
  → Atopy

- Pathogenesis : Ag

  Skin

  Ag + APC's
  ↓
  T Cell
  ↓
  TH2 Cells

Cytokines :   IL − 4   IL − 5
                                  (Recruitment of eosinophils)

Antibody :   IgE antibody

- On Ist exposure : mast cells get sensitized to Ag

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Active space

- On subsequent exposure:

Polymerization

↓

Degranulation

Early phase reaction | Late phase reaction (2-24 hours)

due to preformed mediators (Histamine)

→ Leukotrienes
→ Cytokines
→ Chemokines

↓

- Vasodilation
- ↑ permeability
- Bronchospasm

↓

- Epithelial damage
- Tissue destructinon

- most important cytokines in Type I : IL − 4, 5
- most important cells in Type I : mast cells , eosinophil
- most important Antibody : Ig E
- Earliest mediator released : Histamine
- Stain for mast cell : Toluidine blue

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Type II hypersensitivity   00:11:06

- A/K/A Antibody mediated hypersensitivity
- Examples:
  → mnemonic: My Blood group is RH Positive

  my   → myasthenia gravis

  Blood   → Blood Transfusion Reaction

  Group   → Grave's disease, Goodpasture Syndrome
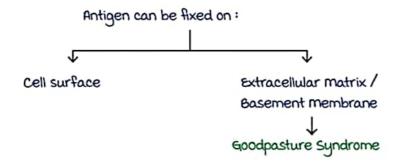
  Is   → ITP, Immune Hemolytic Anemia, IDDM

  R   → Rheumatic fever
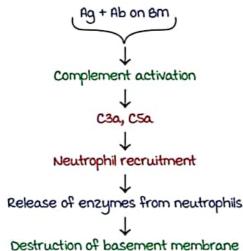
  H   → Hyperacute graft rejection

  Positive → Pernicious anemia
              Pemphigus vulgaris
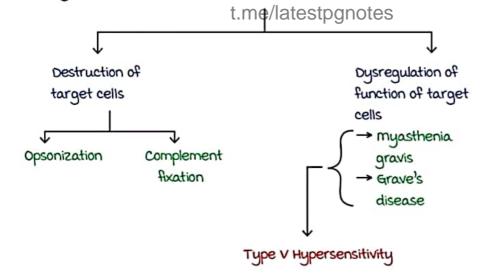
- mechanism:

→ Antibodies which are directed against fixed antigens.

Active space

Antigen can be fixed on :

Cell surface   Extracellular matrix /
                                Basement membrane
                                        ↓
                                Goodpasture Syndrome

- Antigen fixed to Basement membrane (BM) :

                Ag + Ab on BM
                        ↓
            Complement activation
                        ↓
                C3a, C5a
                        ↓
            Neutrophil recruitment
                        ↓
        Release of enzymes from neutrophils
                        ↓
        Destruction of basement membrane

- Antigen fixed on cell membrane:

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Destruction of   Dysregulation of
target cells   function of target
                                   cells
                                        → myasthenia
Opsonization   Complement   gravis
                fixation   → Grave's
                                          disease

            Type V Hypersensitivity

Type III hypersensitivity   00:19:24

- Immune complex mediated
- Examples:

                            ┌→ Type 2 : Hematological
    S → Serum sickness, SLE → Type 3 : Visceral
    H → Henoch–Schonlein purpura
    A → Arthus reaction (classical example)
    R → Reactive Arthritis (Yersinia)
    P → PSGN, PAN

Active space

- Pathogenesis:
1. Formation of immune complex (5 – 7 days)
   Ag + Ab → Immune complex
   most pathogenic immune complex → small, medium sized.
2. Deposition of immune complex
   → m.c sites: Kidney
                 Blood vessels
                 Skin
3. Immune complex mediated tissue injury

Complement activation   Activation of   } 10-14 Days
                               Hageman factor

                    Tissue destruction
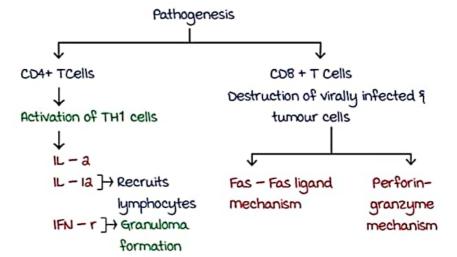
Type IV hypersensitivity reaction   00:24:38

- A/K/A Delayed type hypersensitivity reaction
- Cell mediated (T cells)
- Examples : Granuloma formation
             Tuberculin test
             Lepromin test
             Contact dermatitis
             Acute and chronic graft rejection
             Rheumatoid arthritis
             Multiple sclerosis
             Inflammatory bowel disease
             Psoriasis
             Graft v/s Host Disease (GVHD)

                    Pathogenesis

CD4+ TCells   CD8 + T Cells
   ↓   Destruction of virally infected &
Activation of TH1 cells   tumour cells
   ↓
IL – 2
IL – 12]→ Recruits   Fas – Fas ligand   Perforin-
           lymphocytes   mechanism   granzyme
IFN – r]→ Granuloma   mechanism
           formation

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Active space
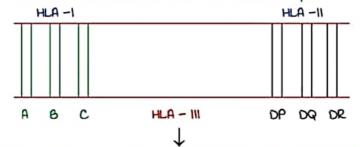
MHC AND GRAFT REJECTION

Major histocompatibility complex (MHC)   00:00:16

- Also known as HLA (Human Leucocyte Antigen)

- Gene is located on short arm of chromosome 6 (or) 6p.

```
        HLA –I                              HLA –II

   A    B    C         HLA – III          DP   DQ   DR
                          ↓
```

Encodes complement protein C_2, C_4, Properdin, Heat shock proteins

HLA – I	HLA – II
• Location Present on all nucleated of cells body and platelets • HLA – A, B, C • Combines with CD8 + T-lymphocytes Nucleated cells of body MHC-I • Structure β2 microglobulin	• Location Only present on APC's (Antigen Presenting Cells) like – dendritic cells, Endothelial cells, fibroblasts • DP, DQ, DR • Combines with CD4 + T-lymphocyte APC MHC-II • Structure
– Antigen binds in a cleft between α_1 and α_2 • Investigation – Detected by Alloantisera • Role – major role in Graft rejection	– Antigen binds between α_1 and β1 • Investigation – Detected by mixed lymphocyte reaction • Role – Graft versus Host disease

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Active space

MHC - Uses

00:07:58

- Uses
  - Paternity Testing
  - Autoimmune Disease, Eg: HLA B-27 – Ankylosing Spondylitis
    HLADR3, DR4 – Diabetes mellitus
  - Transplantation
  - Anthropological Testing

- Transplantation:

  a. HLA matching should be done
  i) Best → HLA – DR > B > A
  [These 3 HLAs should definitely match]
  ii) "000" mismatch → No mismatch on A, B, D
  b. HLA matching is not required for transplantation of
  - Kidney
  - Liver
  - Lung
  - Cornea

Transplants/grafts

00:13:04

1. Isograft/syngeneic graft
   - Transplants from identical twins
2. Autograft
   - Transplants from same individual
3. Allograft
   - Transplants from different individual, but same species
4. Xenograft
   - Transplantation from different species

Graft reactions

00:14:35
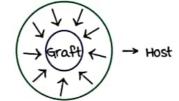
Graft reaction
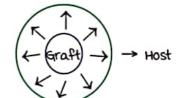
Graft rejection
-If Host is immunocompetent,
the Host cell attack the graft

→ Graft ← → Host

Graft versus Host disease
-If Host is immunosuppressed,
and the Graft attacks Host cells.

← Graft → → Host

Graft rejection

00:17:08
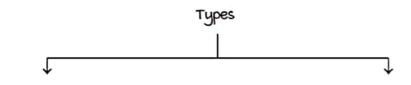
1. Hyperacute Graft rejection

- occurs within mins-hours of transplantation
- Type II hypersensitivity reaction due to preformed antibodies
  • previous blood transfusion
  • previous transplantation
  • multiparous
  • ABO, Rh incompatibility
- Gross:
  Kidney → cyanosed, mottled, flaccid
- microscopy:
  • micro thrombi
  • Fibrinoid necrosis
  • Neutrophilic infiltrates in glomerular capillary vessels
- most commonly seen with Kidney transplantation

2. Acute Graft rejection

- occurs within days-months (<4 months)

Warning: Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with marrow Edition 4 videos.

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Types

Cellular	Humoral
- Acute cellular rejection	Acute Humoral rejection
• caused by i) CD4 + T cells 　　　　 ii) CD8 + T cells	• caused by anti-donor antibodies
• Type IV Hypersensitivity reaction	• Type IV/III
• Responds to ↑ dose of immunosuppressants	But Type II → more common Does not respond to immunosuppressants ∴ Treatment → B-cell depleting agents

Active space
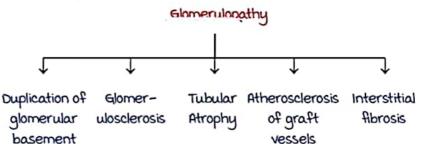
- microscopy:

a. Acute cellular rejection

Pattern

Tubulointerstitial	Vascular
i) Tubulitis	i) Endotheliitis
ii) Interstitial mononuclear Inflammation	

b. Acute humoral rejection

i) Fibrinoid necrosis

ii) Peritubular capillaries

- have deposits of complement breakdown product

C4d → marker for acute humoral rejection

3. Chronic graft rejection

- occurs within years of transplantation

- can be   i) Cell mediated

          ii) Antibody mediated

- Type II/IV hypersensitivity reaction

- microscopy

Glomerulopathy

Duplication of glomerular basement membrane	Glomer- ulosclerosis	Tubular Atrophy	Atherosclerosis of graft vessels	Interstitial fibrosis

Graft Versus Host Disease (GVHD)   00:29:17

- Seen after Bone marrow transplantation (usually)

- Also Known as Runt Disease in animals

- Type IV hypersensitivity reaction
  Types
      i) Acute
          • <6 months
          • Affects → skin (most commonly affected
                    organ) - scleroderma

→ GIT - strictures

→ Liver Cholestatic jaundice

ii) Chronic

• >6 months

• Affects → skin (most commonly affected
organ) – Rash

→ GIT – Bloody diarrhea

→ Liver Cholestatic jaundice

- Y-linked Graft rejection
• Seen when a male gives a graft to a female
• Also known as sex linked graft rejection/Eichwald Slimser effect
• Y chromosome has UT4 gene

Complications of transplantation   00:34:57

1. Infections

  i) CMV (cytomegalovirus) infection → most common

     • owl's eye inclusions

  ii) BK – polyoma virus infection

     • decoy cells

     • PCT → intranuclear basophilic inclusions.

2. Graft versus Host disease

3. Graft rejection

4. ↑ risk of malignancy.

   i) Squamous Cell Carcinoma → HPV associated

   ii) Non-Hodgkin's Lymphoma → EBV associated

   iii) Kaposi's Sarcoma → HHV-8 associated

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Active space

IMMUNODEFICIENCY DISORDERS
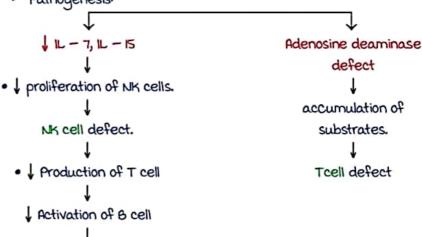
Bruton's hypogammaglobulinemia and DiGeorge syndrome   00:00:17

→ X linked recessive disorder.
→ m ≫ F (Boys > Girls)
→ B cell defect
→ Bruton thyrosine Kinase gene affected.
→ B-cell areas affected.
→ decreased production of IgG antibody
→ Defective opsonization
    ↓
    ↑ risk of infection (pneumococci)

DiGeorge Syndrome

→ defect in long arm of chromosome 22
    ↓
    del 22q"
    ↓
defective development of 3rd and 4th pharyngeal pouches.

    ↓   ↓
  Thymic   Parathyroid
  hypoplasia   hypoplasia

C – cleft lip, cleft palate
A – abnormal facies
T – thymic hypoplasia, T-cell defect
C – cardiac abnormality
H – Hypocalcemia
22 – del 22q‖

→ Pathogenisis: defect in TBX I gene

Wiscott Aldrich syndrome & SCID   00:04:54

→ X linked recessive dissorder.
→ m ≫ F
→ Triad
   1) Eczema
   2) Recurrent infection
   3) Thrombocytopenia
        ↓
   defect in size/number of platelets.

→ Defect in WASP gene.

→ ↓ Igm

Severe combined immune deficiency – SCID

→ First disorder for which gene therapy was successful.

→ Both B and T cell defect.

→ ↑ risk of candida, pneumococci

→ Pathogenesis:

$\downarrow$ IL – 7, IL – 15

- ↓ proliferation of NK cells.

NK cell defect.

- ↓ Production of T cell

↓ Activation of B cell

B cell defect

Adenosine deaminase
defect

accumulation of
substrates.

Tcell defect

Common variable immunodeficiency   00:09:02

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→ occurs in children

→ B cell maturation defect.

→ ↑ risk of – Sinopulmonary infection

B cell ──do not──→ ◯ ──×──→ no. Ig produced
       mature

Plasma cells

– Giardiasis

→ Pathogenesis:

→ ↑ risk of other autoimmune disorders like Rheumatoid arthritis

BAFF

Bcell activating
factor

ICOS

Inducible
costimulator.

and other malignancies

Active space

Isolated Ig A deficiency   00:11:27

→ B cell cannot produce IgA
→ ↓ IgA, ↓ IgG4
→ ↑ risk of GIT, sinopulmonary infection
→ ↑ risk of allergies, anaphylaxis, autoimmune disorders

Hyper IgE syndrome / Job syndrome

→ ↑↑ IgE
→ Autosomal dominant.
→ Pathogenesis: STAT3 gene defect
→ Cold abscess, coarse facial features

Hyper IgM syndrome

→ X – linked recessive disorder.
→ m >>> F
→ ↑↑↑ IgM

defective class switching

↑↑↑ IgM
| attack blood
↓ elements.
– Autoimmune hemolytic anemia
– Autoimmune thrombocytopenia
– Autoimmune leucopenia

↓ IgG, IgA, IgE
↓
recurrent infection
(pneumocystis Jeroveci)

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Ataxia telangiactasia   00:15:11

→ Pathogenisis: ATM gene on chromosome II.
→ Normal ATM gene →

DNA damage sensor
↓
P53 activation
↓
→ mutation of ATM gene → Apoptosis, repair

DNA damage, no repair
↓
↑ risk of neoplasm
immune defects.

Active space
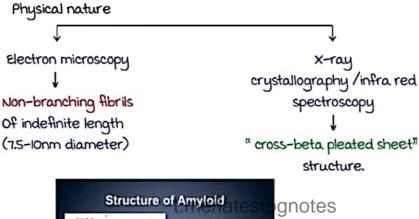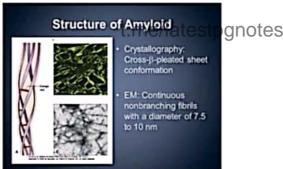
AMYLOIDOSIS

Amyloidosis: 00:00:30
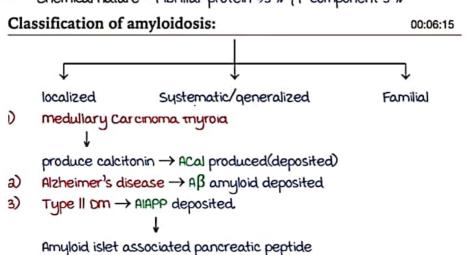
Definition

- Pathologic, proteinaceous, amorphous, extracellular eosinophilic substance deposited in various tissues or organs in various conditions.
- these are hyaline like pink substance.
- misfolded protein.

Physical nature

Electron microscopy
↓
Non-branching fibrils
Of indefinite length
(7.5-10nm diameter)

X-ray
crystallography /infra red
spectroscopy
↓
" cross-beta pleated sheet"
structure.

Structure of Amyloid
- Crystallography: Cross-β-pleated sheet conformation
- EM: Continuous nonbranching fibrils with a diameter of 7.5 to 10 nm

- X-ray crystallography — Apple green birefringence
- Chemical nature - Fibrillar protein 95 % & P component 5 %

Classification of amyloidosis: 00:06:15

localized   Systematic/generalized   Familial

1) medullary Carcinoma thyroid
↓
produce calcitonin → ACal produced(deposited)
2) Alzheimer's disease → Aβ amyloid deposited
3) Type II DM → AIAPP deposited
↓
Amyloid islet associated pancreatic peptide
4) Prion disease → Apr deposited

Active space

Generalized amyloidosis   00:09:43

1) **Primary amyloidosis:**
→   mc type
→   Seen in light chain disorder like multiple myeloma

⬇

     AL amyloid deposited
→   Lambda light chains are commonly deposited

2) **Secondary amyloidosis:**
→   A/K/a reactive systemic amyloidosis
→   Occurs in 2 conditions:

Chronic inflammatory conditions	Chronic malignancies
Bronchiectasis Rheumatoid arthritis TB (mc in India)	Hodgkin's Lymphoma Renal cell carcinoma

→   mc inflammatory conditions leading to secondary amyloidosis –
     Rheumatoid arthritis

Pathogenesis

Chronic inflammation
⬇
Cytokines like IL-1, IL-6
⬇ Act on
Liver
⬇
SAA – Serum amyloid associated protein
⬇
AA type of amyloid

Chronic renal failure/long term dialysis   00:14:37

-    Hemodialysis membrane which was used could not filter a protein
     through it.
⬇
B2 microglobulin– deposited in the body
⬇
- AB2m deposited

Active space

3) Senile/aging amyloidosis
- ATTR (transthyretin) deposited
- Transthyretin protein helps in transportation of thyroxin and retinol
- Transthyretin deposited is normal protein (not mutated)

Familial amyloidosis   00:17:10

Familial amylodotic polyneuropathy
- Autosomal dominant
- Deposition of mutant transthyretin ATTR

Familial mediterranian fever
- Autosomal recessive
- AA deposition.
- "Pyrin" protein.

Disease/Condition	Type of amyloid
① Primary amyloidosis	AL
② Secondary amyloidosis	AA
③ Chronic renal failure/long term dialysis	$A\beta_2 m$
④ Alzheimer' disease	Aβ
⑤ Senile amyloidosis	ATTR
⑥ Familial amyloidotic polyneuropathy	ATTR
⑦ Familial mediterranian fever	AA
⑧ Prion disease	Apr
⑨ Diabetes mellitus	AIAPP
⑩ medullary carcinoma thyroid	ACal

Diagnosis of amyloidosis   00:21:40
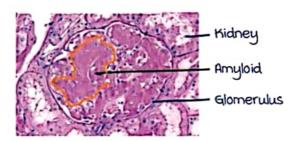
Best or mc test used →
① Abdominal fat pad aspirate
② Rectal biopsy
③ Tongue biopsy
④ Organ biopsy(particular organ)

Stains for amyloid

• H & E stain- pink colour

- Kidney
- Amyloid
- Glomerulus

- PAS Stain- magenta colour
- **Best** stain for amyloid

↓

Congo red Stain

Light microscopy   Polarized light
↓   ↓
Salmon pink   Apple green colour
appearance   birefringence

- methyl violet stain ⎫
- Crystal violet stain ⎬ metachromatic stain
                       ⎭
- Thioflavin S and T — Immunofluorescence
- Gross-stain:
paints the cut surface of organ with Lugol's Iodine
↓
Mahogany brown colour
↓ put H_2SO_4
Blue → amyloidosis

Organ involvement   00:30:37

→   mc organ affected with amyloid — Kidney
→   mc cause of death in primary amyloidosis – heart disease
→   mc cause of death in secondary amyloidosis – renal disease
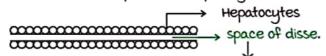
Gross

- Waxy
- Firm in consistency
- Organomegaly

① Kidney

- usually affect mesangium
- Can also affect walls of capillaries and arterioles
- Clinically-nephrotic syndrome

Active space
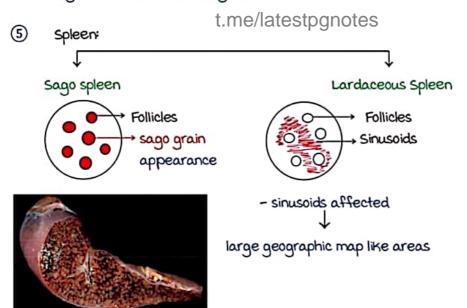
- Renal biopsy

② Liver :
- first affects the "space of disse"

Space b/w hepatocytes and sinusoids

→ Hepatocytes

→ space of disse.

↓

Produce **pressure atrophy** of hepatocytes
- Clinically : Cirrhosis.

③ Heart :
- usually affects Subendocardium
- Clinically :
(1) Arrhythmias
② Right bundle branch block
③ Restrictive cardiomyopathy

④ GIT :
- Tongue involvement : macroglossia

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⑤ Spleen:

Sago spleen

→ Follicles
→ sago grain appearance

Lardaceous Spleen

→ Follicles
→ Sinusoids

- sinusoids affected
↓
large geographic map like areas

→ Follicles affected

GENERAL PATHOLOGY IMAGES

- H & E Biopsy of oesophagus
- Change of stratified squamous epithelium to columnar epithelium
- **metaplasia**
- Diagnosis — Barrett's oesophagus

metaplasia : Reversible change in which one differentiated type of epithelium gets converted to other.

Barrett's Oesphagus

1) Intestinal metaplasia
2) Goblet cells

   (Alcian blue stains mucin to diagnose Barrett's)
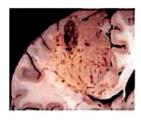
Necrosis - gross specimen   00:04:08

Gross appearance of spleen
- White infarct area
- Wedge shaped
- Coagulative Necrosis (solid organs)

Gross specimen of brain
- Liquefactive necrosis /wet gangrene
- Due to wet gangrene

Gross specimen of lung
- caseous necrosis (cheese like)
  ↓

also seen in fungal ⎡ Histoplasmosis
                    ⎣ coccidiomycosis

Active space
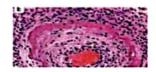
Gross specimen of omentum
- chalky white deposits fat necrosis
  ↓
  Breast, omentum, pancreas

Specimen –blood vessel
- Pinkish material–Fibrin
  ↓
  Fibrinoid necrosis
  ↓
- Type II, III Hypersensitivity reactions
- Malignant hypertension
- Aschoff nodules
- Poly arteritis nodosa

Electrophoresis and pigments   00:10:18
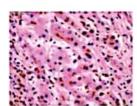
- Polyacrylamide gel electrophoresis (PAGE) DNA electrophoresis
- Smear pattern of necrotic cells
- Stepladder pattern of apoptotic cells
  ↓
  Due to enzyme endonuclease
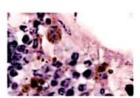
Pigments:
1. Lipofuscin(brown ageing / wear & tear pigment)
2. Hemosiderin
3. melanin
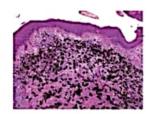
↓
Brown atropy of liver or heart

Hemosiderin:
- multiple blood transfusions
- Thalassemia
- Hemochromatosis

Prussian blue / pearl's stain –special stain

melanin: black pigment
- Stain- masson fontana
- IHC- HMB-45
  S-100
  melan -A
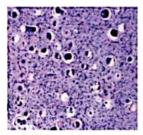
Meningioma   00:17:52

- Dark blue bodies —psammoma bodies
- Foci of dystrophic calcification

Also seen in
1. Papillary Ca thyroid
2. Papillary Ca renal
3. meningioma
4. Serous cystadenocarcinoma
5. Prolactinoma

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Nutmeg liver:
- Gross specimen of liver
- Chronic venous congestion

Red infarct
- Gross specimen of lung
- Wedge shaped infarct
- Seen in organs with dual blood supply
  ↓
  Lung
  Intestine
  ovaries
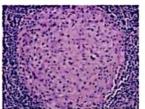
Active space

Warning : Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with marrow Edition 4 videos.

Granuloma

00:21:50
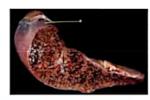
- Epitheloid cells(slipper shaped nucleus)
- Collar of lymphocytes
- Giant cells

Kidney-glomerulus

- Apple green birefringence of amyloid

  congo red stain
- Under polarising microscopy

Sago spleen

- Whitish dots in spleen
- Splenic follicles with amyloid

Lardaceous spleen – amyloid in sinusoids
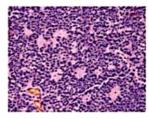
Owl's eye in pathology

00:25:45

Reed Sternberg cell in Hodgkin's lymphoma
(CD 15, CD30+)

- CMV Inclusions
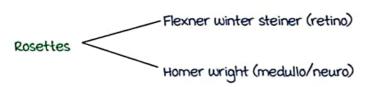
Rosette (neuroblastoma)

- N-MYC over expression
- Small round blue cell tumor
- Rosettes (flower like)

Seen in

1) Neuroblastoma
2) Retinoblastoma
3) Nephroblastoma
4) Medulloblastoma
5) Hepatoblastoma
6) Ewing's sarcoma
7) PNET (primitive neuro ectodermal tumor)
8) Embryonal rhabdomyosarcoma
9) Lymphoma

Active space

Rosettes
— Flexner winter steiner (retino)
— Homer wright (medullo/neuro)
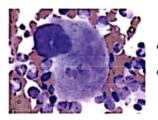
Neutrophil extracellular traps   00:30:22

- NET's
- Fibrillary meshwork(extracellular)
  ↓
  Trap microbes

Emperipolesis (lymphomatoid disorder)
- Cell within a cell appearance
- DD: phagocytosis
  ↓
  cell inside is destroyed

Lymphnode biopsy of a TB patient   00:32:31

-Granulomas
-Epitheloid cells
-Langhans giant cell
-collar of lymphocytes

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Storage disorder   00:34:57

- Ballooning of neuron Tay – sach's disease
- Electron microscopy – onion skin appearance

- Hexosaminidase – α defect
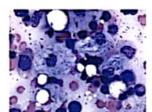
Onion skin appearance in pathology
1) Electron microscopy- Tay sach's
2) X-ray Ewing's sarcoma
3) H & E of malignant hypertension
4) Nerve biopsy CIDP (chronic inflammatory demyelinating polyneuropathy)
5) H & E of primary sclerosing cholangitis
6) Spleen in SLE

Active space

- Electron microscopy
- Alternate black & white
- Zebra bodies

- Niemann pick disease – Sphingomyelinase defect
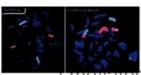
- Bone marrow biopsy
- Crumpled tissue appearance
- Gaucher cells – glucocerebrosidase defect
- PAS +ve

Pseudo Gaucher cell – CML
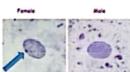
Genetic techniques   00:39:39

FISH

Fluorescent in situ hybridization

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Barr-bodies – inactivated X chromosome
Sample- buccal smear

Shape-drumstick

No. of barr bodies = No. of chromosome – 1

$\male = 0 \quad \female = 1$

Klinefelter's syndrome = 1

Turner's syndrome = 0
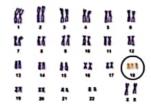
Karyotyping
- Number the chromosomes
- Chromosomal disorders
- G- Banding technique
- metaphase spread
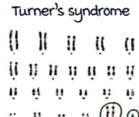
Active space

Patau syndrome

Turner's syndrome

Edward's syndrome

Down's syndrome

Klinefelter's syndrome
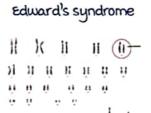
Cri-du-chat syndrome

Neoplasia   00:45:55

Anaplasia – Lack of differentiation

- Pleomorphism
- High N:C ratio
- Hyperchromatic nuclei
- metaphase arrest
- Prominent nucleoli
- Loss of polarity
- Atypical mitosis

Basement membrane (pas stain)

```
        ┌──────────────┴──────────────┐
        ↓                              ↓
     Intact                         Broken
        ↓                              ↓
 Carcinoma in situ               Carcinoma
```


Latest Nobel prize for study on **hypoxia**

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RBC - INTRODUCTION

- RBC size : 7-8 microns

- Life span : 120 days

- RBC shape : Biconcave

- Peripheral blood smear (PBS): ◎ Central 1/3rd pallor

- most important protein to maintain RBC shape: Spectrin

RBC series   00:01:45

Hematopoietic stem cell
↓
Common myeloid Progenitor
↓
Proerythroblast   ↓ Cell size
↓   ↓ Nuclear size
Early Normoblast
(Basophilic Normoblast)
↓
Intermediate Normoblast
(Polychromatic Normoblast)
↓
Late Normoblast
(Orthochromic normoblast)
↓
Reticulocyte (no nucleus)
↓
RBC
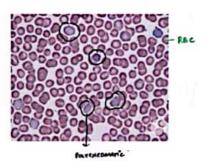
- Extrusion of nucleus : late normoblast

- Reticulocyte : non-nucleated

- Conversion of Reticulocyte to RBC takes 1-2 days

- Hemoglobin production starts in proerythroblast

- Hemoglobin first appears in intermediate Normoblast
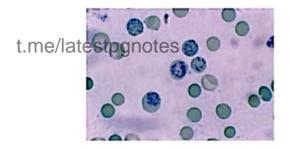
Reticulocytes

00:06:45

- Immediate precursor of RBC

- non nucleated

- Normal Reticulocyte Count : 0.5-1.5%

- Reticulocyte on Romanowsky stain – Polychromasia

← RBC

Polychromatic

- Special Stains

    Supravital Stains → • Brilliant Cresyl Blue

                                   • New methylene Blue

                                → stains the living state of a cell in vitro

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Reticulocyte (reticular meshwork of RNA)

- Causes

    (i) Reticulocytosis (↑ Reticulocyte Count)

            – Acute Blood loss
            – Hemolytic Anemia
            – Response to therapy in iron, vitamin – B12, folate
              deficiency anemia

    (ii) Reticulocytopenia (↓ Reticulocyte Count)

            – Aplastic anemia
            – Cytotoxic drugs
            – Radiation
            – Bone Marrow Suppression

- Corrected Reticulocyte Count

$$= \text{Reticulocyte } \% \times \frac{\text{Patient's Hematocrit (or) Hemoglobin}}{\text{Normal Hb (or) Hematocrit for that age}}$$

- Reticulocyte Production Index (RPI)

$$RPI = \frac{\text{Reticulocyte } \%}{\text{maturation time (depends on PCV)}}$$

PCV		maturation Time
40%	→	I day
30-40%	→	1.5 days
20-30%	→	2 days
<20%	→	2.5 days

- Absolute Reticulocyte Count (ARC)

ARC = Reticulocyte % × RBC count

RBC indices   00:19:00
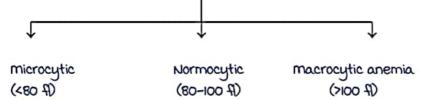
a. mean Corpuscular volume (mcv)

  - Average volume of RBC

  - $mcv = \dfrac{PCV}{RBC}$

  - Normal mcv = 82-96 fl (80-100 fl)

  - Significance of mcv :

Anemia (Based on mcv)

```
          microcytic        Normocytic         macrocytic anemia
          (<80 fl)          (80-100 fl)        (>100 fl)
```

- microcytic Anemia :

  S - Sideroblastic anemia, Lead poisoning

  I - Iron deficiency anemia (IDA)

  T - Thalassemia

  A - Anemia of chronic disease

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134 Hemolytic
Anemias and
RBC
Disorders

20

124
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- macrocytic Anemia

    L – Liver dysfunction

    H – Hypothyroidism

    m – megaloblastic Anemia
       (due to folate/B12 deficiency)

    C – Cytotoxic drugs

- Normocytic Anemia

    Aplastic anemia

    Chronic Renal Failure (CRF)

    Anemia of chronic disease
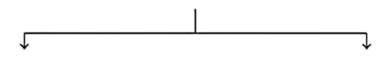
    Hemolytic anemia

    Paroxysmal Nocturnal Hemoglobinuria (PNH)

b. mean Corpuscular Hemoglobin (mCH)

    – Average Hb in a single RBC

    – mCH = $\dfrac{Hb}{RBC\ Count}$

    – Normal mCH – 27 to 32 pg
    – Significance of mCH :

                Anemia (Based on mCH)

    Normochromic   Hypochromic
    (27–32 pg)   (<27 pg)

c. mean Corpuscular Hemoglobin Concentration (mCHC)

    – Hemoglobin (Hb) in a given volume of packed RBC

    – mCHC = $\dfrac{mCV}{mCH}$

    – Normal mCHC = 33–37 gm/dl

    Significance of mCHC

    ↑ mCHC in Hereditary Spherocytosis (due to dehydration)
    Normal mCHC in megaloblastic Anemia
       (Because ↑ volume is proportional to ↑ in the amount of Hb)

Active space
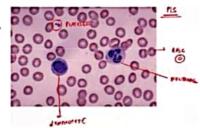
d. Red Cell Distribution Width (RDW)

- RBCs of various size → Anisocytosis.
- RBCs of various shape → Poikilocytosis.
- RDW = co-efficient of variation of RBC size/degree of anisocytosis
- Normal RDW = 11.5 to 14.5%
- Significance of RDW

    - ↑ RDW in IDA
    - Normal RDW in Thalassemia

∴ used to differentiate Iron deficiency anemia & Thalassemia

Peripheral smear findings   00:32:48

Stains used : Romanowsky stains

    - Giemsa stain
    - Leishman stain
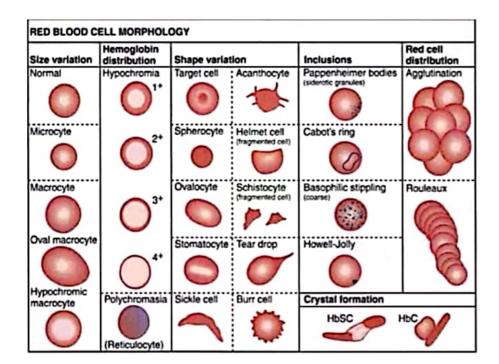
PBS – Giemsa stain

Peripheral Smear Finding		Conditions
1. microcytic Anemia (mcv <80 fl)	◎	S – Sideroblastic Anemia I – IDA T – Thalassemia A – Anemia of Chronic Disease
2. macrocytic Anemia (mcv >100 fl)	◯	L – Liver disease H – Hypothyroidism m – megaloblastic Anemia C – Cytotoxic drugs
3. Spherocytes (No central pallor)	⊘	• Hereditary spherocytosis • Autoimmune Hemolytic Anemia (AIHA) [most common cause] • Blood transfusion reactions • Burns

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Active space
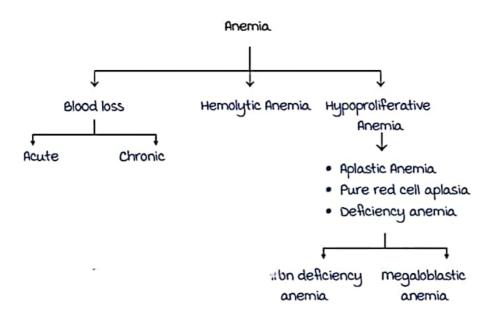
4. Pencil Cell		Iron Deficiency Anemia (IDA)
5. Bite Cell		G6PD deficiency
6. Burr Cell/Echinocyte (Small, regular projections)		• CRF • Uremia • Liver disease
7. Spur Cell/Acanthocyte [sharp, irregular projections]		Abetalipoproteinemia
8. Schistocyte/Helmet/ Fragmented RBC		• microangiopathic Hemolytic Anemia (HUS, TTP, DIC) • Prosthetic Cardiac Valve
9. Sickle Cell		• Sickle cell anemia
10. Target Cell		• Thalassemia (Characteristic) • Liver disease megaloblastic Anemia
11. Tear drop cell (Dacrocyte)		• myelofibrosis • myelophthisis • myelodysplastic syndrome
12. Howell Jolly bodies (remnants of DNA)		• megaloblastic Anemia • Asplenia • Thalassemia
13. Heinz Bodies (precipitates of Hb)		G6PD deficiency
14. Pappenheimer Body		Sideroblastic Anemia
15. Cabot Ring [figure of 8] (composed of microtubules)		• megaloblastic Anemia (B12 deficiency)
16. Rouleaux formation		• multiple myeloma
17. Polychromasia		• Hemolytic Anemia
18. Basophilic Stippling		• Sideroblastic Anemia (Lead Poisoning) • Thalassemia
19. Stomatocyte (Slit like pallor)		• Hereditary Stomatocytosis

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RED BLOOD CELL MORPHOLOGY

Size variation	Hemoglobin distribution	Shape variation		Inclusions	Red cell distribution
Normal	Hypochromia	Target cell	Acanthocyte	Pappenheimer bodies (siderotic granules)	Agglutination
Microcyte	1+ 2+	Spherocyte	Helmet cell (fragmented cell)	Cabot's ring	
Macrocyte	3+	Ovalocyte	Schistocyte (fragmented cell)	Basophilic stippling (coarse)	Rouleaux
Oval macrocyte	4+	Stomatocyte	Tear drop	Howell-Jolly	
Hypochromic macrocyte	Polychromasia (Reticulocyte)	Sickle cell	Burr cell	Crystal formation HbSC HbC	

Active space

HYPOPROLIFERATIVE ANEMIAS

Anemia

↓

Blood loss   Hemolytic Anemia   Hypoproliferative Anemia

Blood loss:
- Acute
- Chronic

Hypoproliferative Anemia:
- Aplastic Anemia
- Pure red cell aplasia
- Deficiency anemia

Deficiency anemia:
- Iron deficiency anemia
- megaloblastic anemia

Hypoproliferative anemias : causes & clinical features   00:02:07

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Hypoproliferative anemias

- Aplastic anemia
- Pure red cell aplasia

Aplastic Anemia

- Generalized bone marrow suppression
- ↓ Hb
- ↓ TLC
- ↓ Platelet
- ↓ Reticulocyte

Causes of Aplastic anemias

Inherited
Fanconi's anemia

Acquired
Drugs
Radiation
Viruses
Bone marrow suppression

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Clinical features

- ↓ Hb → Pallor, Fatigue
- ↓ TLC → ↑ infections, Fatigue
- ↓ Platelet → bleeding tendency
- Splenomegaly is absent
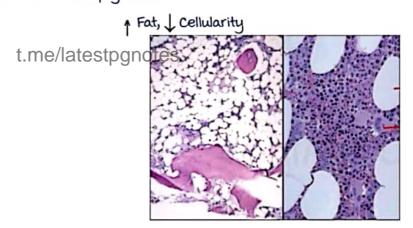
Lab diagnosis of aplastic anemia 00:05:49

- Hb ↓
- TLC ↓
- Platelet ↓
- Reticulocyte ↓
- Peripheral smear : Normocytic, Normochromic Anemia
  Pancytopenia
- Bone marrow aspirate : Dry tap
- Bone marrow biopsy : IOC

↑ Fat, ↓ Cellularity

Severe aplastic anemia, pure red cell aplasia 00:09:08

Criteria

- Bone marrow cellularity <25%
- And any two of the following:
  Corrected Reticulocyte count < 1%
  Absolute Neutrophil Count (ANC) <500/μ^3
  Platelet count <20,000/μ^3
- Very severe aplastic anemia:
  Same as severe aplastic anemia with ANC <200/μ^3

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Treatment

- Stem cell transplantation (ideal)

- GM = CSF (Granulocyte monocyte Colony Stimulating Factor)

- Antithymocyte globulin

Pure red cell aplasia

- ↓ erythroid precursors

- ↓ Hb, ↓ Reticulocyte

Causes:

Hereditary	Acquired
↓	↓
Diamond Blackfan syndrome	• Parvo virus B19
	• Thymoma
	• Large granular lymphocytic leukemia
	• B cell disorders
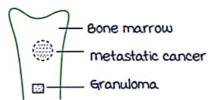
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Myelophthisic anemia   00:14:00
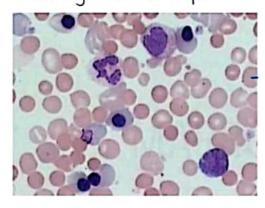
Cause : Space occupying lesions of Bone marrow

- Bone marrow
- metastatic cancer
- Granuloma
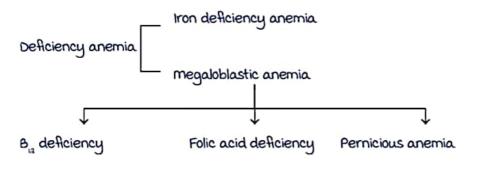
Characteristic features : Tear drop cells

Leucoerythroblastic blood picture

MEGALOBLASTIC ANEMIA

Deficiency anemia
- Iron deficiency anemia
- megaloblastic anemia

B_{12} deficiency   Folic acid deficiency   Pernicious anemia

Vitamin B_{12} deficiency   00:01:38

Vit B_{12} - A/K/A cyanocobalamine

Daily requirement 2-3 μg

mechanism of absorption

Diet (Vit B12)

↓

Stomach

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Vit B12 + Haptocorrin (salivary gland)

↓

Duodenum

Haptocorrin is removed with the help of pancreatic proteases
Vit. B_{12} + Intrinsic factor → parietal cells of stomach

↓

Terminal ileum (max absorption)
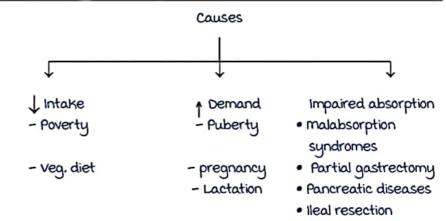
Vit. B_{12} gets absorbed via Cubilin receptors

Vit. B_{12} gets transported via Transcobalamin II

Active space

144 Hemolytic
Anemias and
RBC
Disorders

22

132
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Causes of B₁₂ deficiency   00:06:58

Causes

↓ Intake
- Poverty

- Veg. diet

↑ Demand
- Puberty

- pregnancy
- Lactation

Impaired absorption
• malabsorption
  syndromes
• Partial gastrectomy
• Pancreatic diseases
• Ileal resection

MC worm causing B₁₂ deficiency anemia :

Fish tapeworm/Diphyllobothrium latum

Biochemical reactions catalyzed by Vit. B₁₂   00:11:20

I. d UMP ⌐
    d TMP ←⌐   * UMP – Uridyl monophosphate
                         TMP – Thymine monophosphate

Deficiency of Vit B₁₂

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↓ Thymine Synthesis
↓
Nuclear cytoplasmic asynchrony
↓
maturation arrest
↓
Pancytopenia

a. Homocysteine ——Vit B₁₂——→ methionine

    ↑ Homocysteine
    ↓
    Arterial thrombosis (Atherosclerosis)

3. methyl malonyl CoA ——Vit B₁₂——→ Succinyl CoA

                    component of myelin sheath
                    ↓
        Neurological complications in vit B₁₂ deficiency

Active space

Clinical features of B$_{12}$ deficiency

00:16:38

- Pallor, fatigue, ↑ risk of infections, splenomegaly, jaundice

- Neurological complications like SCD (Subacute combined degeneration)

Lab diagnosis

Hb
TLC   } ↓
Platelet

MCV ↑ (>100 fl)
MCH ↑
MCHC - N

Peripheral Smear :

RBC   - macro-ovalocytes

- Cabot rings (figure of 8 ; microtubule)

- Howell Jolly body
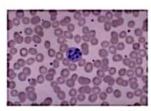
- Basophilic stippling (fine)

WBC - Hypersegmented neutrophils (>5 lobes)
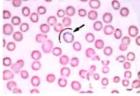
Criteria for hypersegmented neutrophils

00:21:45

5% neutrophils with 5 or more lobes
single neutrophil with 6 or more lobes

Bone marrow aspirate
↓

Fine basophillic stippling

Erythroid hyperplasia
(reversal of myeloid : Erythroid ratio)

Megaloblasts

00:25:40
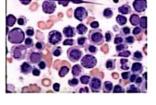
- Large erythroid precursors
- Sieve like chromatin
WBC - Giant metamyelocytes & band forms.

Biochemical tests

S. methyl malonyl CoA
S. Homocysteine   } ↑
S. LDH

Active space

146 Hemolytic
Anemias and
RBC
Disorders

22

134
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Vit B$_{12}$ assay ↓

Rx : Vit B$_{12}$ oral or i.m.

monitor treatment using reticulocyte count

Megaloblastic anemia due to folate deficiency & Pernicious anemia

00:28:16

- Folate source - green leafy vegetables

- Site of absorption: Jejunum

- Polyglutamate

    ↓

    monoglutamate (absorbed)

- Neurological complications seen in B$_{12}$ deficiency are absent in folate deficiency

Pernicious anemia

- Type II hypersensitivity reaction

- Autoimmune disorder

Types of antibody
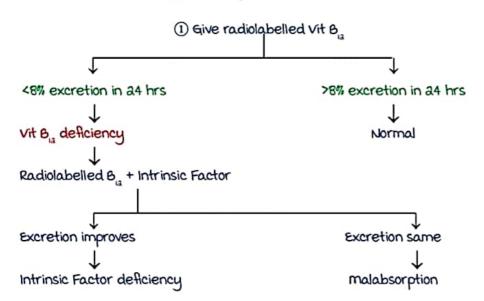
Type I	Type 2	Type 3
Blocks binding of B$_{12}$ to Intrinsic Factor	Prevents binding of B$_{12}$ + Intrinsic Factor to ileal receptor	Antiparietal cell antibody

Clinical features

- Beefy tongue
- Atrophic glossitis
- ↑ risk of other autoimmune disorders
- ↑ risk of gastric adenocarcinoma (occurs in fundus)

Active space

Schilling test

00:35:34
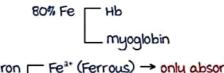
– to find the cause of B_{12} deficiency

① Give radiolabelled Vit B_{12}

<8% excretion in 24 hrs	>8% excretion in 24 hrs
↓	↓
Vit B_{12} deficiency	Normal

↓

Radiolabelled B_{12} + Intrinsic Factor

Excretion improves	Excretion same
↓	↓
Intrinsic Factor deficiency	malabsorption

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Active space

IRON DEFICIENCY ANEMIA

- MC nutritional disease in the world

- most common type of nutritional anemia in India

- Normal diet : 10-20 mg of Fe

$$80\% \text{ Fe} \begin{cases} \text{Hb} \\ \text{myoglobin} \end{cases}$$
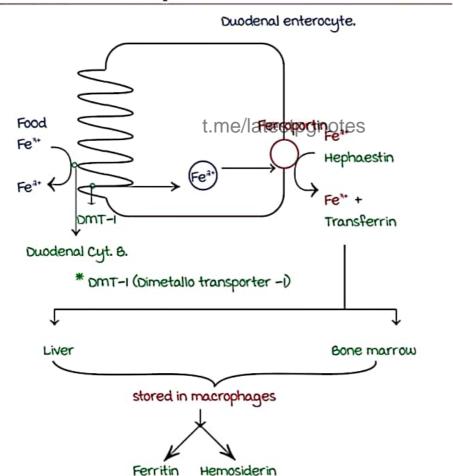
$$\text{Iron} \begin{cases} Fe^{2+} \text{ (Ferrous)} \rightarrow \text{only absorbable form} \\ Fe^{3+} \text{ (Ferric)} \end{cases}$$

MC site of absorption of Fe - Duodenum

Mechanism of Fe absorption   00:03:02

* DMT-1 (Dimetallo transporter -1)

Active space

Hepcidin   00:09:20
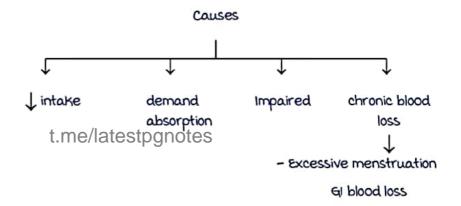
- molecule produced by liver
- master regulator of Fe metabolism
- Acute phase reactant
- Negative Fe regulator
  - ↑ Hepcidin → ↓ Fe
  - ∴ Hepcidin binds to ferroportin and causes its degradation

Transferrin

Ideally one transferrin can bind 6 mol of Fe.
Practically 1 transferrin carries 2 mol of Fe
Transferrin saturation = 2/6 = 1/3 = 33%.

Causes of Fe deficiency anemia   00:14:15

```
                        Causes
                          |
      ┌──────────┬────────┴────────┬──────────────┐
      ↓          ↓                 ↓              ↓
  ↓ intake    demand          Impaired      chronic blood
             absorption                         loss
                                                 ↓
                                        - Excessive menstruation
                                          GI blood loss
```

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MC worm causing Fe deficiency anemia is Hookworm/Ancylostoma duodenale

Genetic ⎡ mutation DMT-1
        ⎣ Atransferrinemia

Clinical features

- Pallor, fatigue, dyspnea, palpitations

- Koilonychia (spoon shaped) nails
- Pica

Plummer Vinson Syndrome ⎡ Atrophic glossitis
                       ⎢ Oesophageal webs
                       ⎣ Fe deficiency anemia

Active space
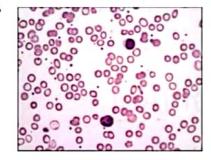
Diagnosis of Fe deficiency anemia   00:18:26

Hb ↓   mcv ↓

TLC N   mcH ↓

PLT N/↑   mcHC ↓

Peripheral smear – microcytic hypochromic picture ± pencil cells ± target cells

Fe studies

- Serum Fe ↓
- S. Ferritin ↓
- S. transferrin saturation ↓
- TIBC (Total Fe binding capacity) ↑

Bone marrow Fe ↓
   Stain "Prussian blue"
   FEP – Free erythrocyte protoporphyrin
   Fe + protoporphyrin ⟶ Heme.
   RDW: ↑ (anisocytosis)
   used to differentiate Fe deficiency anemia from thalassemia.
most sensitive/earliest to decrease: S. Ferritin.

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Treatment of Fe deficiency anemia   00:24:26

monitoring of Fe therapy: Reticulocyte count
↓
on successful therapy, reticulocytosis within 5–7 days

$$\text{mentzer index} = \frac{mcv}{RBC \ count}$$

> 13 Fe deficiency anemia
< 13 Thalassemia

$$\frac{\text{S. Transferrin receptor}}{\text{Log S. Ferritin}}$$
   > 1.5 : Fe deficiency anemia
   < 1.5 : Anemia of chronic disease

Active space

152 Hemolytic
Anemias and
RBC
Disorders

23

139
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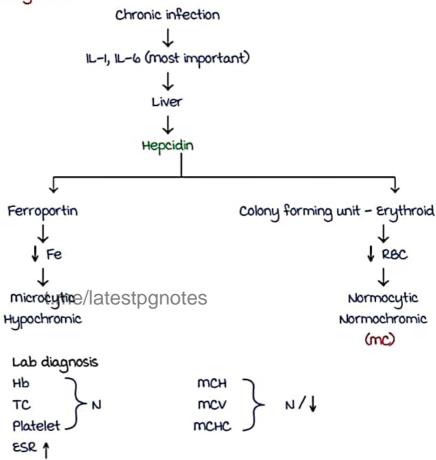
Anemia of chronic disease   00:28:03

Causes

1. Chronic infections - TB
2. Chronic inflammatory - RA , SLE
3. Chronic neoplasm - multiple myeloma
4. Idiopathic

Pathogenesis

$$Chronic\ infection$$
$$\downarrow$$
$$IL-1,\ IL-6\ (most\ important)$$
$$\downarrow$$
$$Liver$$
$$\downarrow$$
Hepcidin

Ferroportin   Colony forming unit - Erythroid
$$\downarrow$$ $$\downarrow$$
↓ Fe   ↓ RBC
$$\downarrow$$ $$\downarrow$$
microcytic   Normocytic
Hypochromic   Normochromic
                              (mc)

Lab diagnosis

Hb ⎤   mCH ⎤
TC ⎬ N   mcv ⎬ N/↓
Platelet ⎦   mCHC ⎦
ESR ↑

Peripheral smear - Normocytic normochromic/microcytic hypochromic
Fe profile   S. Fe ↓
                  S. Ferritin ↑ / N
                  TIBC ↓
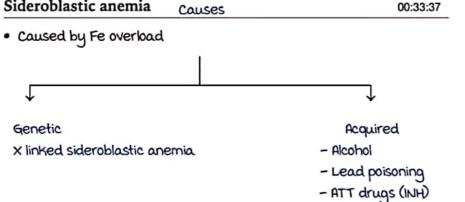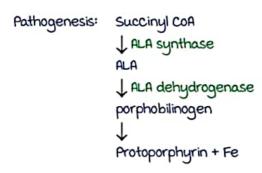
$$\dfrac{S.\ Transferrin\ receptor}{Log\ S.\ Ferritin}$$ ⎡ > 1.5 : Fe deficiency anemia
                                      ⎣ < 1.5 : Anemia of chronic disease

Sideroblastic anemia   Causes   00:33:37

- Caused by Fe overload

```
                              |
          ┌───────────────────┴───────────────────┐
          ↓                                        ↓
       Genetic                                  Acquired
  X linked sideroblastic anemia                - Alcohol
                                               - Lead poisoning
                                               - ATT drugs (INH)
```

Pathogenesis: Succinyl CoA
                   ↓ ALA synthase
                 ALA
                   ↓ ALA dehydrogenase
                 porphobilinogen
                   ↓
                 Protoporphyrin + Fe
                         \   /
                          \ /   Ferrochelatase
                           ↓
                         Heme
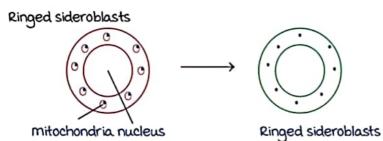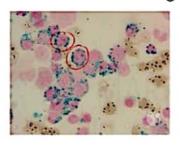
↓ Heme synthesis
↑ Fe accumulation   ⇒ Sideroblastic anemia

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Ringed sideroblasts

mitochondria nucleus   Ringed sideroblasts

Fe profile :   S. Fe ↑
                S. Ferritin ↑

S. Transferrin saturation ↑

S. TIBC ↓

Rx – Iron chelators

Diagnosis –

Hb ↓

$\left.\begin{array}{l} MCV \\ MCH \\ MCHC \end{array}\right\} ↓$

Peripheral smear – Coarse basophilic stippling with microcytic hypochromic

Picture.

S. Fe ↑

S. Ferritin ↑

S. TIBC ↑

S. Transferrin saturation ↓

Lateral points   00:42:34

- Corrected reticulocyte count

$$= Reticulocyte\ \% \times \frac{patient\ Hb}{N.\ Hb}$$

- Prussian blue principle

    Ferrocyanide to ferric ferrocyanide

- History of cancer
  Pancytopenia
  Leucoerythroblastic blood picture $\left.\right\}$ myelophthisic anemia
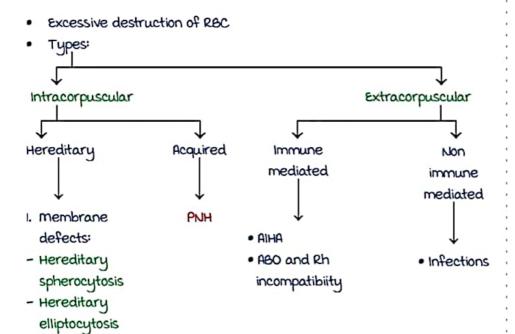
Fanconi's anemia   00:45:31

• Pancytopenia with hypercellular marrow.
  Pancytopenia with hypocellular marrow
    1. PNH
    2. Hairy cell leukemia
    3. myelophthisis

Active space

HEMOLYTIC ANEMIA - 1

- Excessive destruction of RBC
- Types:

```
                              Types
                    ┌───────────┴───────────┐
                    ↓                       ↓
            Intracorpuscular         Extracorpuscular
              ┌──────┴──────┐         ┌──────┴──────┐
              ↓             ↓         ↓             ↓
          Hereditary    Acquired   Immune         Non
                                   mediated       immune
              ↓             ↓        ↓          mediated
```

1. membrane   PNH
   defects: • AIHA
- Hereditary   • ABO and Rh   • Infections
  spherocytosis   incompatibiity
- Hereditary
  elliptocytosis

2. Enzyme deficiency
   - G6PD deficiency
   - Hexokinase deficiency

3. Hemoglobinopathies
   - Sickle cell anemia
   - Thalassemia

Intravascular hemolysis:

Destruction of RBC within blood vessel.

Extravascular hemolysis:

Destruction of RBC outside blood vessels, in the liver or spleen.

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Clinical presentation of hemolytic anemias   00:05:20

- Pallor   -   Hb ↓
- Jaundice   -   ↑ unconjugated bilirubin
- Splenomegaly
- Pigment gall stones → in chronic hemolysis.

Active space

156 Hemolytic
Anemias
and RBC
Disorders

24

143
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Lab tests:

Hb ↓
↑ unconjugated bilirubin
Reticulocyte count ↑
↑ LDH

In intravascular hemolysis:
Hemoglobinuria
Hemosiderinuria
methalbuminemia
↓ S. Haptoglobin
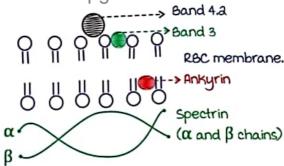
Intravascular hemolysis	Extravascular hemolysis
1. Hepatosplenomegaly +/–	++
2. Hemoglobinuria +/–	–
3. Hemosiderinuria +	–
4. S. haptoglobin ↓ +	+/–

Hereditary spherocytosis (HS) - Pathogenesis   00:11:19

Autosomal dominant (75%)

Pathogenesis:

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Proteins maintaining RBC membrane stability:
Spectrin
Ankyrin
Band 3
Band 4.2

mutation in any of these proteins

↓

Unstable RBC membrane

↓

RBC assumes spherical shape

↓

Trapped in splenic sinusoids

↓

Gets destroyed

↓

. Extravascular hemolysis

- m.c protein defect in hereditary spherocytosis: Ankyrin
  m.c protein defect in elliptocytosis: Spectrin
  most important protein for maintaining RBC shape: spectrin
  mutation not seen : Glycophorin
  (most abundant protein on RBC membrane)

Hereditary spherocytosis - Dignosis and treatment   00:18:21

Clinical features:

Pallor
Jaundice
Splenomegaly
↑ Risk of gallstones

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Lab tests :

Hb ↓
Reticulocyte count ↑
Unconjugated bilirubin ↑
MCHC ↑
Peripheral smear(P/S):

Spherocytes – smaller cells
          – No central pallor
Also seen in : AIHA (autoimmune hemolytic anemia)
          Burns
          Blood transfusion reaction

m.c. cause of spherocytes : AIHA.
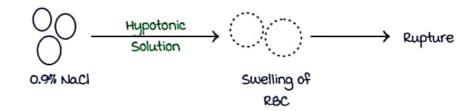
Osmotic fragility test
Suspend RBC in increasing concentration of normal saline
Isotonic solution: 0.9% NaCl

Active space

158 Hemolytic
Anemias
and RBC
Disorders

24

145
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Normal RBCs

0.9% NaCl → Hypotonic Solution → Swelling of RBC → Rupture

Normal hemolysis, starts at 0.5% and stops at 0.3% NaCl
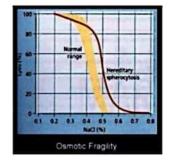
In HS,
   spherical RBC swell and rupture at higher concentration of normal saline (0.8% NaCl)

   Curve shifts to the right

In thalassemia,
   Curve shifts to the left
   (due to rigid target cells)

Osmotic Fragility

Flow cytometric analysis of RBC membrane protein:
   - best test for HS

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Treatment:

   Splenectomy (treatment of choice)
   - Howell jolly bodies seen in smear post splenectomy.

Glucose - 6 - phosphate dehydrogenase deficiency   00:27:36
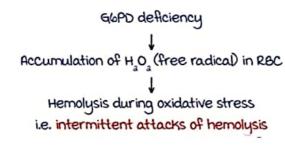
X-linked recessive inheritance
   males >>> females
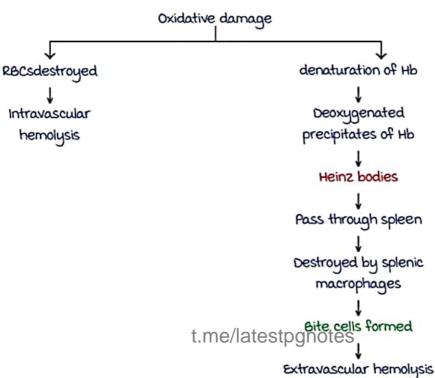
Pathogenesis:

HMP shunt:

Glucose 6 - phosphate → G6PD → 6 - Phosphogluconate
                         H_2O_2 → H_2O

G6PD deficiency

↓

Accumulation of H_2O_2 (free radical) in RBC

↓

Hemolysis during oxidative stress
i.e. intermittent attacks of hemolysis

Oxidative damage

RBCs destroyed	denaturation of Hb
↓	↓
Intravascular hemolysis	Deoxygenated precipitates of Hb
	↓
	Heinz bodies
	↓
	Pass through spleen
	↓
	Destroyed by splenic macrophages
	↓
	Bite cells formed
	↓
	Extravascular hemolysis

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Factors causing hemolysis in G6PD deficiency:

Chronic infections
Drugs like anti malarials
Fava beans

G6PD deficiency-diagnosis and treatment   00:35:31
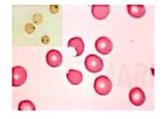
Clinical features:

- Pallor, jaundice → episodic/intermittent
- No splenomegaly or gallstones
- Hemoglobinuria

Lab Dignosis:

Hb ↓
Reticulocyte count ↑
Unconjugated bilirubin ↑

Active space

160 Hemolytic
Anemias
and RBC
Disorders

24

147
Leave Feedback

- Peripheral smear:
  Bite cells/Degmacytes

- On vital stain: Heinz body

- methemoglobin reduction test
- G6PD enzyme assays

Treatment:

Self limiting disease.
Avoid oxidative stress.

Oxidative damage affects → old RBCs
G6PD deficiency, sickle cell anemia and thalassemia → protective
against P. falciparum

Hemoglobinopathies-sickle cell anemia   00:41:40

Normal Hb in adult:

HbA	-	$\alpha_2\beta_2$	-	95-97% (mc)
HbF	-	$\alpha_2\gamma_2$	-	< 1%
HbF	-	$\alpha_2\delta_2$	-	2 - 3.5%

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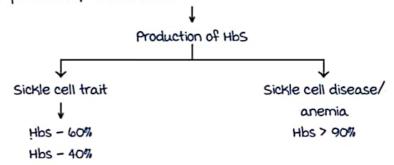
Defective production of any of these Hb – Hemoglobinopathies

Sickle cell anemia (SCA)
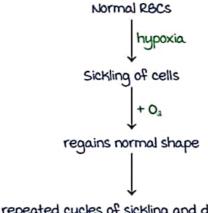
- Autosomal recessive

Pathogenesis:

missense point mutation – glutamic acid replaced by valine at the
6th position of β-chain of Hb.
↓
Production of HbS

Sickle cell trait   Sickle cell disease/
↓   anemia
Hbs – 60%   Hbs > 90%
Hbs – 40%

Activi 3ce

Normal RBCs

↓ hypoxia

Sickling of cells

↓ + O₂

regains normal shape

↓
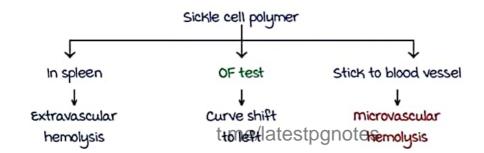
repeated cycles of sickling and desickling

Sickle cell polymer formation
3S : ↓ solubility
sticky
stiff

Sickle cell polymer

In spleen	OF test	Stick to blood vessel
↓	↓	↓
Extravascular hemolysis	Curve shift to left	microvascular hemolysis

Factors affecting sickling:

↑ sickling	↓ sickling
• Hypoxia	HbF
• Dehydration	Clinical features of SCA don't manifest until 6 months of age.
• Acidosis (↓ pH)	

Sickle cell anemia- clinical features and complications   00:51:28

Clinical features:

Pallor, jaundice
Splenomegaly ——later——→ Autosplenectomy
(due to splenic infarcts)

Active space

162 Hemolytic
Anemias
and RBC
Disorders

24

149
Leave Feedback
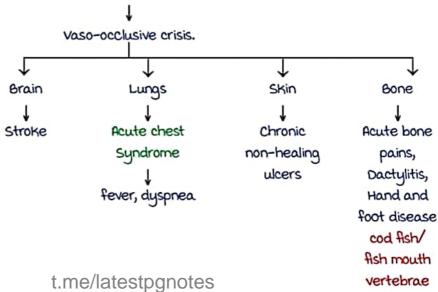
X-ray skull:

Crew-cut/Hair on end appearance
(due to extramedullary hematopoiesis)

Complications:

1. microvascular occlusions
   ↓
   Vaso-occlusive crisis.

Brain	Lungs	Skin	Bone
↓	↓	↓	↓
Stroke	Acute chest Syndrome	Chronic non-healing ulcers	Acute bone pains, Dactylitis, Hand and foot disease cod fish/ fish mouth vertebrae
	↓		
	fever, dyspnea		
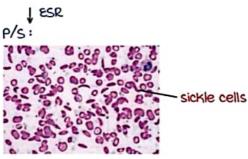
2. Aplastic crisis.
   Parvovirus B19 infection ⟶ aplasia

3. Sequestration crisis
   Entire spleen sequestered with blood
   ↓
   Hypovolemia (dangerous)

Sickle cell anemia - Lab diagnosis   00:57:55

Lab diagnosis

↓ ESR
P/S:
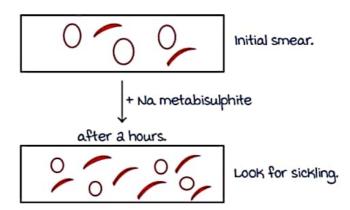
— sickle cells

Tests for sickle cell anemia
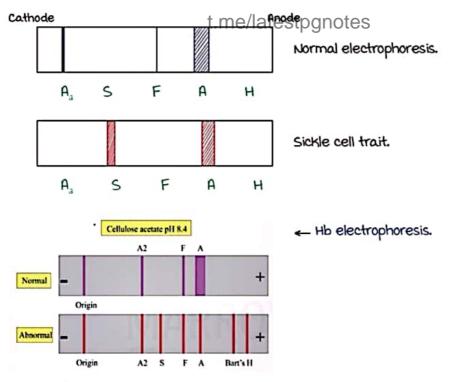
I. sickling test
  - add sodium metabisulphite (O_2 consuming agent) to patients blood sample → artificial hypoxia.

Initial smear.

+ Na metabisulphite

after 2 hours.

Look for sickling.

- ↑ false positive rate
- cannot differentiate sickle cell disease and trait

II. Hemoglobin electrophoresis
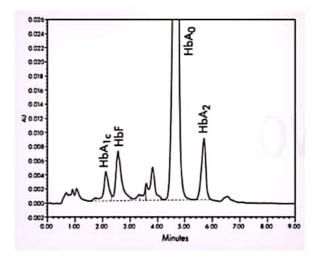
Principle : movement of different Hb varies according to solubility in a medium.

Cathode   Anode

Normal electrophoresis.

A_2 S   F   A   H

Sickle cell trait.

A_2 S   F   A   H

← Hb electrophoresis.

Cellulose acetate pH 8.4

A2   F   A

Normal —   +

Origin

Abnormal —   +

Origin   A2 S F A Bart's H

• Cannot quantify HbS

III. High performance liquid chromatography
   Principle: Differential adsorption of various Hb.
   IOC for hemoglobinopathies.

Quantification of different Hb possible.

Sickle cell anemia- Treatment

01:07:46

- Stem cell transplant (ideal)
- Hydroxyurea (↑ HbF)

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HbSC disease

HbS and HbC present
HbC: glutamic acid replaced by lysine at 6th position in β-chain.

Active space

HEMOLYTIC ANEMIA - 2

Thalassemia   00:00:12

- m.c in mediterranean.
- in India → Punjabis, Sindhis.
- Autosomal recessive (AR)
- Types:

β – thalassemia	α – thalassemia
↓ β – chain synthesis	↓ α – chain synthesis.
HbA – αa βa	HbA – αa βa
↓	↓

- aβ chains – coded by 4β genes on ch. II
- due to mutations
- more common

- aα - chains coded by 4α – genes on ch. 16
- due to gene deletions

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β - Thalassemia   00:03:13

β – thalassemia major	β – thalassemia intermedia	β – thalassemia minor

Terminologies
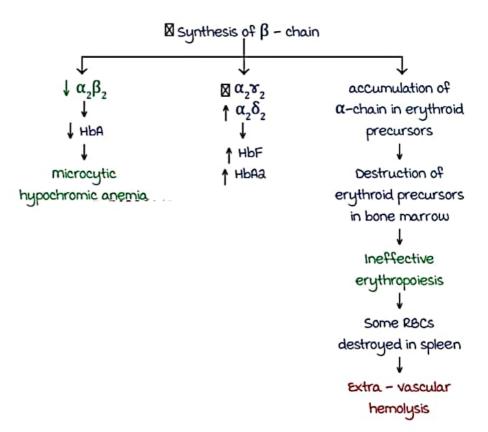
β → normal
β⁺ → Partial deficiency of β-chain
β⁰ → complete deficiency of β-chain

Active space

Pathogenesis

$$\boxtimes \text{Synthesis of } \beta - \text{chain}$$

$\downarrow \alpha_2\beta_2$	$\boxtimes \alpha_2\gamma_2$ $\uparrow \alpha_2\delta_2$	accumulation of α-chain in erythroid precursors
$\downarrow$ HbA	$\downarrow$	$\downarrow$
microcytic hypochromic anemia	$\uparrow$ HbF $\uparrow$ HbA2	Destruction of erythroid precursors in bone marrow
		$\downarrow$
		Ineffective erythropoiesis
		$\downarrow$
		Some RBCs destroyed in spleen
		$\downarrow$
		Extra – vascular hemolysis

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β - Thalassemia major   00:08:08

- marked reduction in β-chain synthesis
- Clinically: Pallor, Jaundice, Splenomegaly,
  $\uparrow$ gallstones, Crew-cut skull
  h/o repeated blood transfusions
  Frontal bossing, Flat nasal bridge
  ↳ Chipmunk / Thalassemic facies

Lab diagnosis:
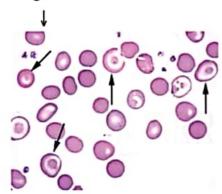
Hb $\downarrow\downarrow$
Retic count $\uparrow\uparrow$
MCV
MCH } $\downarrow$
MCHC
RDW – normal (differentiate from iron – deficiency anemia)

Peripheral smear

- microcytic hypochromic red cells
- Target cells
- Basophilic stippling
- Howell Jolly bodies

Target cells

↓

Basophilic stippling
Teardrop cell
Basophilic stippling
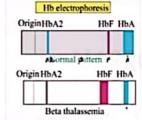
Hb. electrophoresis: ↑ HbF
                      (thick fetal band)

Hb electrophoresis
OriginHbA2   HbF HbA

Abnormal pattern ↑ ↑
OriginHbA2   HbF HbA

Beta thalassemia

High Performance   : ↑ HbF (diagnostic)
Liquid Chromatography ↑ HbA₂

Treatment:
      repeated transfusion
      stem cell transplant

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m.c. cause of death : Fe overload due to repeated transfusions.

β-Thalassemia minor/trait   00:15:13

Clinically – Normal/Asymptomatic

Lab diagnosis :   Hb ↓   (8-10 gm%)
                  mcv
                  mcH   } Ⓝ or ↓
                  mcHc

Peripheral smear : Target cells
Fe profile : Ⓝ
Hb electrophoresis : ↑ HbA₂
HPLC : Ⓝ HbA₂ : 2-3.5%
      4-9% HbA₂ → diagnostic of thalassemia trait
      > 9% HbA₂ → HbE disease

Active space

- Genetic counselling done.

Iron deficiency anemia	Thalassemia trait
RDW ↑↑↑	RDW − Ⓝ or ↑
mentzer index > 13	< 13
HbA_2 : 2-3.5 %	HbA_2 : 4-9 %
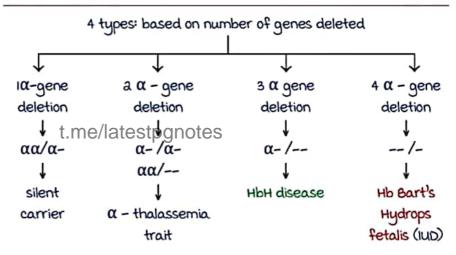
- mass screening of thalassemia patients:

    NESTROF test
    ↓
    Naked Eye Single Tube Redcell Osmotic Fragility Test

- Curve of osmotic fragility in thalassemia and sickle cell anemia → shifts to left

α - Thalassemia   00:22:39

4 types: based on number of genes deleted

1α-gene deletion	2 α - gene deletion	3 α gene deletion	4 α - gene deletion
↓	↓	↓	↓
αα/α-	α- /α-	α- /--	-- /-
↓	αα/--	↓	↓
silent carrier	↓ α - thalassemia trait	HbH disease	Hb Bart's Hydrops fetalis (IUD)

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HbH disease:

    α - gene deletion
    ↓
    β4 - tetramer formation
    ↓
    high affinity for O_2
    ↓
    hypoxia

Active space

Paroxysmal nocturnal hemoglobinuria   00:25:53

- Only acquired intra corpuscular defect

Pathogenesis

    Normal:

      PIGA gene (Phosphatidyl Inositol Glycan A) in nucleus

        ↓

      encodes for GPI anchored proteins

CD55	CD59	C8 binding proteins
(Decay accelerating factor)	(membrane inhibitor of reactive lysis)	

      ↓

    - ↓ complement activity

In PNH

      PIGA gene mutation

        ↓
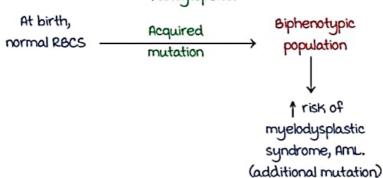
↓ Synthesis of CD55, CD 59 (most important), C8 binding proteins

      ↑ complement activity

        ↓

    complement mediated cell lysis

        ↓

      Pancytopenia

At birth, normal RBCS →(Acquired mutation)→ Biphenotypic population

        ↓

      ↑ risk of myelodysplastic syndrome, AML. (additional mutation)

PNH - diagnosis and treatment   00:31:46

Clinical features:

- Nocturnal hemoglobinuria (25%)

sleep ——→ ↓ pH ——→ ↑ complement activity

- Pancytopenia
- Thrombosis   :   Budd Chiari Syndrome.

170 Hemolytic
anemias and
RBC
Disorders

25

157
Leave Feedback

m.c. cause of disease related death in PNH

Lab diagnosis :

- Hb, TLC, platelet
- Hypercellular bone marrow
- Ham's test / Acidified Serum Lysis test
- Sucrose Lysis Test
- Best test for PNH : Flow cytometric evaluation of RBC
  membrane proteins

Treatment :
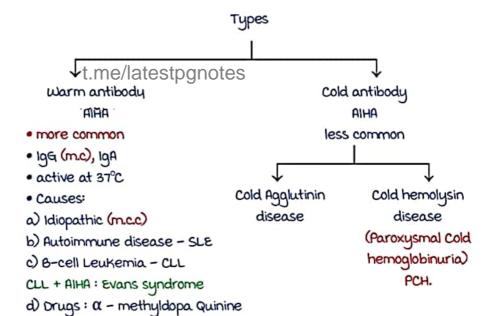
- Stem cell transplant
- Eculizumab – complement inhibition.

Autoimmone hemolytic anemia (AIHA)   00:36:40

- Type II hypersensitivity reaction.
- due to antibodies against RBC membrane proteins

Types

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Warm antibody
AIHA

- more common
- IgG (m.c), IgA
- active at 37°C
- Causes:
a) Idiopathic (m.c.c)
b) Autoimmune disease – SLE
c) B-cell Leukemia – CLL
CLL + AIHA : Evans syndrome
d) Drugs : α – methyldopa Quinine

Cold antibody
AIHA

less common

Cold Agglutinin
disease

Cold hemolysin
disease
(Paroxysmal Cold
hemoglobinuria)
PCH.

Cold agglutinin disease

- Antibody active at 4°C
- IgM ab against i antigen of RBC

Cold hemolysis disease

- IgG antibody against P
  antigen of RBCs
Donath Landsteiner antibody.

Causes of cold antibody AIHA

- Infectious mononucleosis, Mycoplasma

Lab tests:

- Peripheral smear : Spherocytes.
- Coomb's test positive
- RBC clumps (agglutination) in cold antibody AIHA

Microangiopathic hemolytic anemia (MAHA)   00:42:35

1. Hemolytic Uremic Syndrome (HUS)
2. Thrombotic Thrombocytopenic Purpura (TTP)
3. Disseminated intravascular coagulation (DIC)

HUS and TTP

Pentad:
1. Fever
2. MAHA
3. Thrombocytopenia
4. Renal abnormality - m.c in HUS
5. Neurological abnormalities - mostly in TTP

HUS:

- in children
- h/o gastroenteritis
- Types

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Typical
- due to E. coli O157: H7 Shigella

Atypical.
- deficiency of factor H, I or properdin.

TTP:
- defect in ADAM TS 13 protein (breaks down high molecular weight multimers of vWF)

In TTP:

mutation of ADAM TS 13

↓

Accumulation of high molecular weight multimers of vWF.

↓

Thrombosis

↓

↓ platelets

Clinical features of HUS and TTP

- Intravascular hemolysis
- P/S : schistiocytes, helmet cells, fragmented red cells.
- ↑ LDH

Active space

Intravascular and extravascular hemolysis

00:47:38

Causes of:

Intravascular hemolysis	Extravascular hemolysis
• MAHA — HUS	• G6PD deficiency
TTP	• Hereditary spherocytosis
DIC	• AIHA
• Prosthetic cardiac valves	• Sickle cell anemia
• mechanical injury to RBC	• Thalassemia
• G6PD deficiency	
• Plasmodium falciparum	
• Paroxysmal cold hemoglobinuria	
• PNH	

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Active space

ACUTE LYMPHOBLASTIC LEUKEMIA

Acute leukemia   00:00:12

- WHO defines acute leukemia as:
  > 20% blasts in bone marrow and / peripheral blood.
- FAB defines acute leukemia as :
  > 30% blasts in bone marrow and / peripheral blood.
- FAB — is based on morphology of blasts.
- WHO — is based on markers

Difference between lymphoblasts and myeloblast   00:03:10

Lymphoblast	Myeloblast
(1) Smaller size	(1) Larger size
(2) Scanty cytoplasm	(2) Moderate cytoplasm
(3) No granules	(3) Granules present
(4) Auer rods (−)	(4) Auer Rods ⊕
(5) Coarse, clumped chromatin	(5) open up/homogenous chromatin.
(6) Inconspicuous nucleoli	(6) 2-5 prominent nucleoli
(7) Stain: PAS +ve	(7) Stain: MPO, Sudan black B, NSE +ve
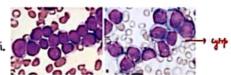
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→ Auer rods — morphological hallmark of a myeloblast
→ Nuclear feature (chromatin) — most important differentiating features.
→ Myeloblast have: large cell, moderate cytoplasm
→ Granules (+), prominent nucleoli.
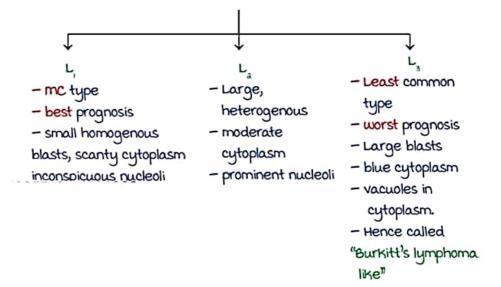
Acute lymphoblastic leukemia (ALL)   00:10:28

→ MC cancer in children.
→ Age: 2-9 years.
→ clinically:
  - Anemia → Pallor fatigue
  - ↓ number of WBC's → ↑ infections.
  - ↓ Platelets → Bleeding tendency.
  - Hepatosplenomegaly: due to extramedullary haematopoiesis.
  - Bone pain (sternal tenderness)
  - CNS involvement
  - Testicular involvement
  - Lymph node involvement

Active space

FAB classification of ALL   00:14:55

L₁
- mc type
- best prognosis
- small homogenous
blasts, scanty cytoplasm
inconspicuous nucleoli

L₂
- Large,
heterogenous
- moderate
cytoplasm
- prominent nucleoli

L₃
- Least common
type
- worst prognosis
- Large blasts
- blue cytoplasm
- vacuoles in
cytoplasm.
- Hence called
"Burkitt's lymphoma
like"

WHO classification of ALL   00:18:20
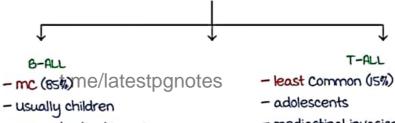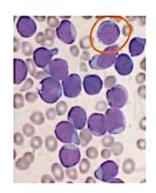
B-ALL
- mc (85%) t.me/latestpgnotes
- Usually children
- No mediastinal invasion
- loss of function mutation
- In PAX -5, E2A or EBF
gene
- Better prognosis.

T-ALL
- least Common (15%)
- adolescents
- mediastinal invasion
present
- gain of function mutation
in NOTCH I gene
- poor prognosis

Lab diagnosis:
① Complete blood count
Hb ↓
TLC ↓ or ↑
Plc ↓
② Peripheral smear
> 20% lymphoblasts
③ Bone marrow aspiration
>20% lymphoblasts.
→ In Aleukemic leukemia
P/S – No blasts

Active space

27 Acute
Lymphoblastic
Leukemia

Leave Feedback
162
181
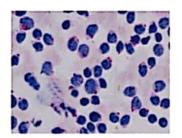
BM aspiration - > 20% blasts.
Stain: PAS ⊕ DOT/BLOCK Positivity.
→ Because in AML – m6 – diffuse
PAS + ve
→ T-ALL → Acid phosphatase +ve

Markers and treatment of ALL   00:25:27

markers:
→ Both PRE B + PRE T lymphoblasts → TdT +
TdT – Terminal deoxynucleotidyl transferase
→ B-ALL – CD19, PAX-5, CD10
→ T-ALL – CD1, CD2, CD5, CD7
CD10-CALLA – Common ALL antigen.

Treatment:
① Stem cell transplantation
② Chemotherapy
– Vincristine
– L Asparaginase
– Prednisolone
– Doxorubicin
→ Intrathecal methotrexate for CNS Prophylaxis

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Prognostic factors in ALL   00:29:03

Good prognosis	Bad prognosis.
→ Age: 2-9 years	→ <1 year to> 10 years
→ Females	→ males
→ Whites	→ blacks
→ L1 subtype	→ L2, L3 subtype
→ B-ALL	→ T-ALL
→ CNS, Testis, spleen	→ CNS, Testis, spleen
→ Hyperdiploidy (> 50 chromosome)	→ hypodiploidy
(mc – cytogenetic abnormality)	→ t (9:22); fusion protein size – 190 KDA
→ Trisomy 4, 7, 10, t (12:21)	→ TLC > 1,00,000/ml
→ TLC <1,00,000/ml	

Active space

ACUTE MYELOID LEUKEMIA

Introduction   00:00:10

- Age = 15 – 45 years
- Clinically =
  - non-specific : pallor, fatigue, increased infections, bleeding tendencies, hepatosplenomegaly.
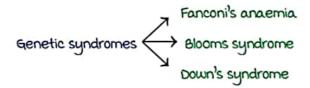
    Usually no CNS, testes or lymph node involvement
  - Specific : Gum hyperplasia / bleeding

    DIC (raised d-dimer, raised FDPs or abnormal coagulation profile)

Chloroma or granulocytic sarcoma
- Risk factors : Chemicals, radiation

Genetic syndromes
- Fanconi's anaemia
- Blooms syndrome
- Down's syndrome

FAB classification of Acute Myeloid Leukemia (AML)   00:03:35

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AML– m$_0$	AML	undifferentiated
AML– m$_1$	AML	without maturation
AML– m$_2$	AML	with maturation
AML– m$_3$	Acute	promyelocytic leukemia
AML– m$_4$	Acute	myelomonocytic leukemia
AML– m$_5$	Acute	monocytic leukemia
AML– m$_6$	Acute	erythro leukemia
AML– m$_7$	Acute	megakaryoblastic leukemia
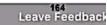
- AML– mo $\Rightarrow$ MPO $\ominus$

- AML– m$_2$ $\Rightarrow$ pathogenesis : t (8;21)

    most common FAB type of AML
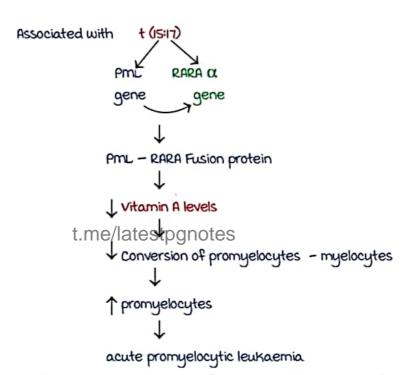
    maximally associated with chloroma

Active space
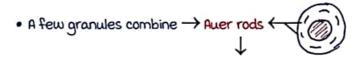
- Chloroma

- also called as myeloblastoma or granulocytic sarcoma
- greenish in color because it is MPO⊕
  comprises of myeloblasts
  soft tissue involvement of AML
- most common site – eye (⊕proptosis)
- Arbiskov cells – presence of monocytes in a chloroma

AML- M3 : Acute promyelocytic leukaemia   00:10:23

Associated with   t (15:17)

PmL   RARA α
gene   gene

↓

PML – RARA Fusion protein

↓

↓ Vitamin A levels

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↓

↓ Conversion of promyelocytes – myelocytes

↓

↑ promyelocytes

↓

acute promyelocytic leukaemia

- Promyelocytes have plenty of granules in cytoplasm and are usually hyperygranular (azurophilic granules)
  A hypogranular variant also exists

- A few granules combine → Auer rods ←

↓

criss cross pattern of Auer rods = FAGGOT CELLS

Auer rods and faggot cells are hallmarks of AML- m$_3$

- Granules contains thrombotic material

$\downarrow$

Breakage of granules causes its release

$\downarrow$

Disseminated Intravascular Coagulopathy (DIC)

- Treatment of AML- m_3 :

   All — trans retonic acid (ATRA) + arsenic trioxide
- Best prognosis of all AML types

AML- M4, M5   00:19:12

- Stains $\Rightarrow$ MPO $\oplus$

   NSE $\oplus$, a stain for monoblasts
- Strongly associated with gum bleeding
- AML- m_5 is the most common AML in infants
- associated with skin involvement: leukaemia cutis

AML - M6 and AML-M7   t.me/latestpgnotes   00:21:16

- AML- m6 $\Rightarrow$ also called Di Gugleimo disease

   Diffuse PAS$\oplus$
- AML- m7 – secrete PDFG (Platelet desired growth factor)

   $\hookrightarrow$ myelofibrosis

      $\hookrightarrow$ dry tap on bone marrow aspirate

   $\Rightarrow$ associated with Down's syndrome

   $\Rightarrow$ CD 41+, CD 61+

   $\Rightarrow$ budding cytoplasmic margins can be seen

   $\Rightarrow$ Least common type of AML

Active space

WHO classification of AML   00:24:40

① AML with recurrent genetic abnormalities

   a) AML with t (8:21) RUN X1/ETO fusion gene

              ⌐──────────────────────→ AML– m$_2$

   b) AML with t (15:17) PML / RARA fusion gene

              ⌐──────────────────────→ AML– m$_3$

   c) AML with inv. 16 or t(16:16) CBFB/MYH11 fusion gene

              ⌐──────────────────────→ AML– m$_4$
                                              eosinophilia

   d) AML with t (11q;v) MLL fusion gene.

   e) AML with normal cytogenetics and mutated NPM

② AML therapy related

③ AML with MDS like features

④ AML not otherwise specified (NOS)

   – includes all FAB types except APML or AML–m$_3$
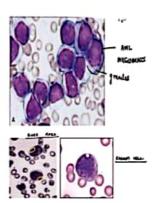
Lab diagnosis of AML   00:28:53

• CBC   ↓ Hb

         ↓ TLC

         ↓ Platelets

• Peripheral smear and Bone marrow aspirate
                >20% myeloblasts
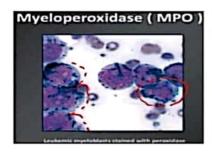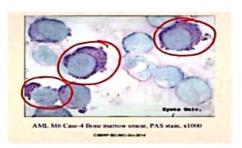
Stains :   ① MPO + (myeloperoxidase)
            ② SBB + (Sudan Black B)
            ③ NSE + (monoblasts)

AML M6 is diffuse PAS+

Myeloperoxidase (MPO)

Leukaemia myeloblasts stained with peroxidase

AML M6 Case-4 Bone marrow smear, PAS stain, x1000

markers : CD 13, 33, 117 +
          MPO +

- Diagnosis of AML can be made if blasts are <20%
  when there is
          t (8:21) or
          t (15:17) or   } <20% blasts
          inv. 16

Treatment
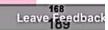
t.me/latestpgnotes   00:34:43

• Definitive treatment – Stem cell transplantation
  For AML- M3 – ATRA +Arsenic trioxide

- Biphenotypic leukaemia:
    – If the blasts show both myeloid lineage markers as well as lym-
    phoid lineage markers, it is called biphenotypic
    – myeloid lineage markers : CD 13, 33,117 +, MPO+
  lymphoid lineage markers   : CD 19, 20, 10+, PAX 5+
                                CD 2,3,5, 7+

Active space

HODGKIN'S LYMPHOMA

WHO classification of lymphoid disorders   00:00:25

```
                    │
    ┌───────┬───────┼───────┬───────┐
    ↓       ↓       ↓       ↓       ↓
    I       II      III     IV      V
```

I	II	III	IV	V
Precursor B-cell disorders	Precursor T-cell disorders	Peripheral B-cell disorders (mature)	Peripheral T-cell disorder	Hodgkin's lymphoma (HL)
↓	↓	↓	↓	
B-ALL	T-ALL			

Peripheral B-cell disorders (mature):
- CLL/SLL chronic & small lymphocytic lymphoma
- mantle cell lymphoma
- Follicular lymphoma
- Diffuse large B-cell lymphoma
- marginal zone lymphoma
- Burkitt's lymphoma
- Hairy cell leukemia
- Plasma cell disorder
- lymphoplasmacutic lymphoma

Peripheral T-cell disorder:
- Extranodal lymphoma
- Anaplastic large cell lymphoma
- Angioimmunoblastic lymphoma
- mycosis fungoides
- Adult T-cell leukemia

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Difference between Hodgkin's and non-Hodgkin's lymphoma   00:05:27
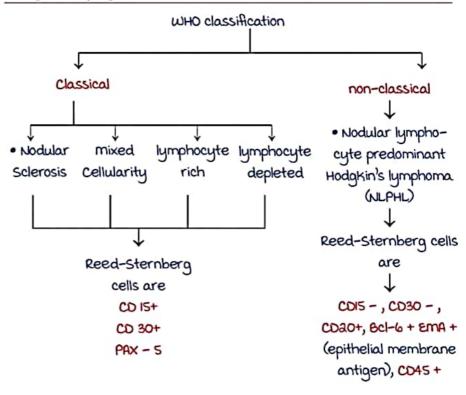
Hodgkin's lymphoma	Non-Hodgkin's lymphoma
1) Bimodal age distribution 15-20 yrs, elderly	• Can occur at any age
2) Cervical lymph node enlargement	• Generalized lymphadenopathy
3) Contiguous spread	• Non contiguous spread
4) Reed – Sternberg cells in an inflammatory back-ground – Present	• Absent Reed – Sternberg cells

Active space

Hodgkin's lymphoma – WHO classification   00:09:06

WHO classification

Classical — non-classical

Classical:
- Nodular Sclerosis
- mixed Cellularity
- lymphocyte rich
- lymphocyte depleted

↓

Reed-Sternberg cells are
CD 15+
CD 30+
PAX – 5

non-classical:
- Nodular lymphocyte predominant Hodgkin's lymphoma (NLPHL)

↓

Reed-Sternberg cells are

↓

CD15 – , CD30 – , CD20+, Bcl-6 + EMA + (epithelial membrane antigen), CD45 +

Warning : Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with marrow Edition 4 videos.

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Hodgkin's lymphoma – pathogenesis   00:13:28

Ebstein barr virus associated
↓
Produces LMP-1 (latent membrane protein – 1)
↓
Activation of NF-KB pathway (growth signalling pathway)
↓
↑ cell proliferation
↓
Hodgkin's lymphoma

C/F – Fever, night sweats, weight loss
↓
Pel ebstein fever
- Painless cervical lymph node enlargement
- Paraneoplastic syndrome — AA type of Amyloid
- Pain induced by alcohol ingestion
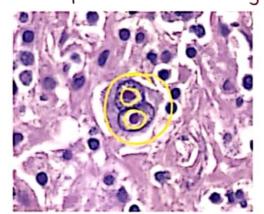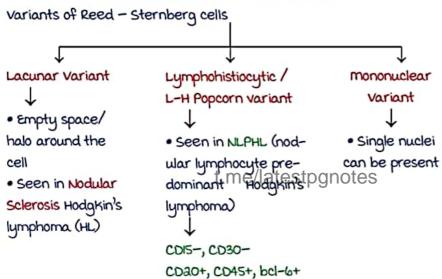
Reed Sternberg cells
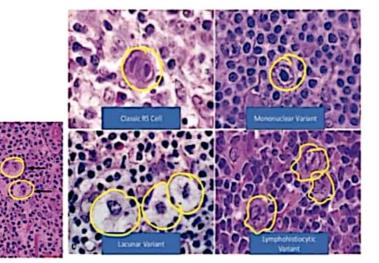
00:16:40

- Large cells (15-45 μ)
- Binucleate
- Prominent eosinophilic macronucleoli — Owl's eye appearance

Variants of Reed – Sternberg cells

Lacunar Variant

↓

- Empty space/ halo around the cell
- Seen in Nodular Sclerosis Hodgkin's lymphoma (HL)

Lymphohistiocytic / L-H Popcorn variant

↓

- Seen in NLPHL (nodular lymphocyte predominant Hodgkin's lymphoma)

↓

CD15−, CD30−
CD20+, CD45+, bcl-6+
EMA +

mononuclear Variant

↓

- Single nuclei can be present

Classic RS Cell

Mononuclear Variant

Lacunar Variant

Lymphohistiocytic Variant

Lacunar Variant

Active space
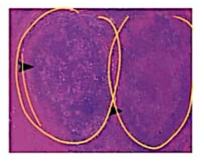
Nodular Sclerosis Hodgkin's lymphoma   00:22:56

- m.c HL in the world
- males = Females
- mediastinal involvement can be seen
- Uncommonly associated with EBV
- Lacunar Reed – Sternberg cells (R – S)
- CD15+, CD30+
- On histopathological examination (H & E) – nodules
                                                sclerosis
                                                Lacunar R–S cells

- Best prognosis among classical forms of HL

Mixed cellularity Hodgkin's lymphoma   00:26:41

- m.c type in India
- males > Females
- No mediastinal involvement
- 70% cases are EBV associated (maximum association)
- Classical
- Maximum association with B symptoms
- On H & E – mixed population of cells

Lymphocyte rich and lymphocyte depleted
Hodgkin's lymphoma   00:28:44

Lymphocyte rich
- Large number
  of lymphocytes
- Few R–S cells

Lymphocyte depleted
- Least common
- worst prognosis
- Can be EBV/HIV as-
  sociated

Active space

Nodular lymphocyte predominant Hodgkin's lymphoma 00:30:16

- Non-classical HL
- R-S cells – CD15-, CD30-, CD20+, CD45, EMA+, Bcl – 6 +
- L-H or popcorn R-S cells
- Never associated with EBV
- Best Prognosis

NODULAR SCLEROSIS	MIXED CELLULARITY	LYMPHOCYTE RICH	LYMPHOCYE DEPLETED	LYMPHOCYTE PREDOMINANT
MC TYPE OF HL	MC TYPE IN INDIA		ASSOCIATED WITH HIV	
INCIDENCE EQUAL IN M & F	M>F	M>F	M>F	M>F
RS CELL VARIANT IS LACUNAR CELL	MAXIMUM NO OF RS CELLS	MONO NUCLEAR RS CELLS	MUMMIFIED, NECROBIOTIC	POPCORN CELLS
CD 15+, CD 30+	CD 15+, CD 30+	CD 15+, CD 30+	CD 15+, CD 30+	CD 20 +, BCL 6+ & EMA +
NOT ASSOCIAT WITH EBV	ASSOCIATED WITH EBV			NOT ASSOCIAT WITH EBV
EXCELLENT PROGNOSIS	PROGNOSIS VERY GOOD	GOOD	POOR PROGNOSIS	EXCELLENT PROGNOSIS

- R-S cells are not 100% diagnostic

    ↓

R-S cells in an inflammatory background is diagnostic

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Treatment of Hodgkin's lymphoma
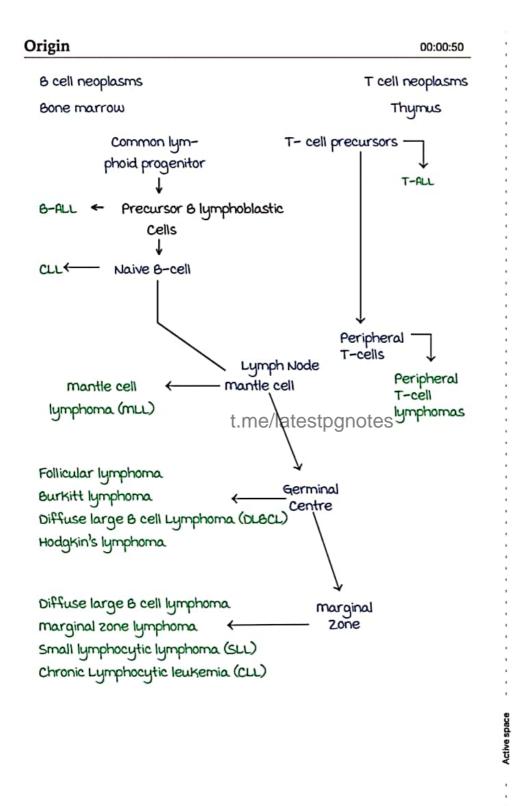
    A – Adriamycin
    B – Bleomycin
    V – Vinblastine
    D – Dacarbazine

Ann Arbor Staging

- **Stage I:** Single lymph node region (I) or single extralymphatic organ or site (I$_E$)

- **Stage II:** ≥ 2 lymph node regions on same side of diaphragm (II) or with limited, contiguous extra lymphatic tissue involvement (II$_E$)

- **Stage III:** both sides of diaphragm involved, may include spleen (III$_S$) or local tissue involvement (III$_E$)

- **Stage IV:** multiple/disseminated foci involved with ≥ 1 extralymphatic organs (i.e. bone marrow)

(A) or (B) designates absence/presence of "B" symptoms
*(E) Localized, solitary involvement of extralymphatic tissue, excluding liver and bone marrow

Active space

NON HODGKIN'S LYMPHOMA

Origin   00:00:50

B cell neoplasms   T cell neoplasms

Bone marrow   Thymus

Common lym-   T- cell precursors
phoid progenitor
                                        T-ALL
↓

B-ALL ← Precursor B lymphoblastic
            Cells
            ↓

CLL ← Naive B-cell

                                        Peripheral
                                        T-cells

mantle cell ← Lymph Node   Peripheral
lymphoma (MLL)   mantle cell   T-cell
                                   lymphomas

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Follicular lymphoma
Burkitt lymphoma   Germinal
Diffuse large B cell Lymphoma (DLBCL) Centre
Hodgkin's lymphoma

Diffuse large B cell lymphoma   marginal
marginal zone lymphoma ←   Zone
Small lymphocytic lymphoma (SLL)
Chronic Lymphocytic leukemia (CLL)

Active space

Chronic Lymphocytic Lymphoma /Small Lymphocytic Lymphoma   00:02:50

- Chronic lymphocytic leukemia

        or

Small lymphocytic lymphoma (when lymph nodes are involved)

- Age: 6th or 7th decade
- most common type of chronic leukaemia in elderly
- Diagnostic criteria: absolute lymphocytosis >5000/mm³
- Clinically : lymphadenopathy, hepatosplenomegaly

                            [warm antibody autoimmune haemolytic anaemia]

- Cytogenetic : most common cytogenetic abnormality – del 13$_q$

         On ch 3, a tumor suppressor micro RNA

                  mir-15-a   mir-16-1

         Others: Del 11$_q$, 17$_p$

- Lab diagnosis:
  - CBC → Hb =   Normal
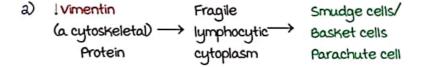
        TLC   —   increased

        Platelet   —   Normal or decreased

Peripheral smear   →

P/s CLL
- RBCs
- SMUDGE CELL /BASKET/ PARACHUTE CELL
- ↑ SMALL LYMPHOCYTES
- CONVENT GIRLS APP
Nucleus

i) Increased number of small lymphocytes

    Convent girls repetition appearance

a)   ↓Vimentin   Fragile   Smudge cells/
       (a cytoskeletal) → lymphocytic → Basket cells
        Protein   cytoplasm   Parachute cell

- Bone marrow aspirate : ↑ Lymphocytes

Lymph node biopsy:-

① Lymph node architecture is replaced by large number of small

cells with inconspicuous nucleoli

② In between them are activated lymphoid cells

↓

proliferation centres
(pathognomic of CLL)
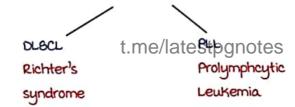
- Flow cytometry:- CD 19+, CD 20+

CD 5+ ⎱ It helps to differentiate CLL
CD 23+ ⎰ from mantle cell lymphoma

- Rai & Binet staging system is used

CLL Can transform

DLBCL   ALL
Richter's   Prolymphcytic
syndrome   Leukemia

t.me/latestpgnotes
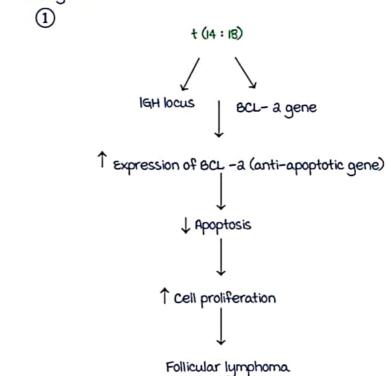
- Prognostic markers that indicate bad prognosis

• Increased serum levels of β2 microglobulin, CD 23, LDH

• Presence of notch-I mutation

Presence of 11q , 17p deletion

• Increased expression of ZAP 70

Active space
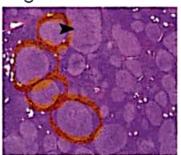
Follicular lymphoma   00:17:14

- Pathogenesis

  (1)

$$t\ (14:18)$$

IGH locus   BCL- 2 gene

↑ Expression of BCL -2 (anti-apoptotic gene)

↓ Apoptosis

↑ Cell proliferation

Follicular lymphoma

  (2)   90% cases — MLL gene mutation

- most common types of indolent NHL in the western world
- Lymph node biopsy:-

  (1)   cells are arranged in follicles

  (2)   2 types of cells : centrocytes and Centro blasts

Centrocytes & Centroblasts

Active space

Centrocytes are small cells with cleaved nucleus contours

Centro blasts are large cells with prominent nucleoli

- Bone marrow aspirate

  paratrabecular lymphoid aggregates

- Tumor markers: CD19+ , CD20+

  BCL2 + (is used to differentiate follicular
  lymphoma from hyperplasia)
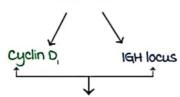
  30-50% can transform into DLBCL

Mantle cell lymphoma   00:24:20
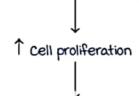
- seen in elderly

- males >> Females

- Present as painless lymphadenopathy

- Characteristic way of spread to GIT with polypoid

  Lesions : Lymphomatoid polyposis (GIT)

- Pathogenesis:

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  $t (11 : 14)$

  Cyclin D_1 IGH locus

  ↑ Expression of cyclin D_1 gene

  ↓

  ↑ Cell proliferation

  ↓
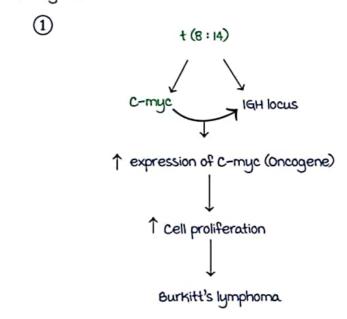
  mantle cell Lymphoma

- Lymph node biopsy:- small cleaved lymphocytes
  [CLL is CD 5+ and CD 23+]
- markers   CD5+

         CD23-

         cyclin D_1
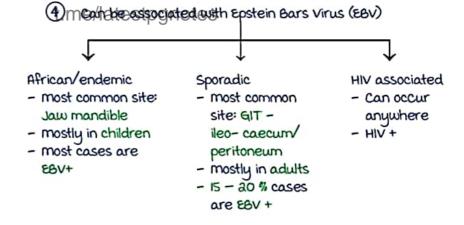
in cyclin D_1 negative MCL — SOX- 11 best marker

Active space

Burkitt's lymphoma   00:29:00

- Pathogenesis:-

  ①

  t (8 : 14)

  C-myc   IGH locus

  ↑ expression of C-myc (Oncogene)

  ↑ Cell proliferation

  Burkitt's lymphoma

  ② t (2:8)

  ③ t (8:22)

  ④ Can be associated with Epstein Bars Virus (EBV)

African/endemic	Sporadic	HIV associated
- most common site: Jaw mandible	- most common site: GIT – ileo- caecum/ peritoneum	- Can occur anywhere
- mostly in children	- mostly in adults	- HIV +
- most cases are EBV+	- 15 – 20 % cases are EBV +	

- Lymph node biopsy:-

  Starry sky appearance

  → sky (lymphoid)

  } MACROPHAGES (stars)

  Index of cell proliferation — high Ki67, MIB –I Score

- Bone marrow aspirate

(BMA)

- large cells
- coarse chromatin
- Royal blue cytoplasm
- cytopl. vacuoles
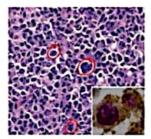
- Tumor markers :- CD19+, CD 20+,

    BCL-6+

- It is a very aggressive chemo sensitive tumor

    It is the most common cause of tumor lysis syndrome
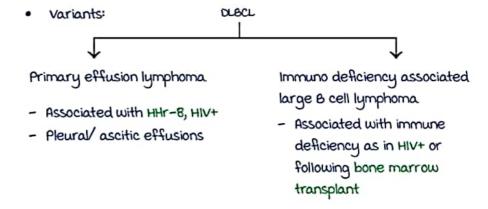
DLBCL – Diffuse large B cell lymphoma   00:38:50

- Age: elderly
- It is the most common type of NHL in India
- Pathogenesis :   ①   Dysregulation of BCL-6

                  ②   myc translocation

                  ③   t (14:18)

- Lymph node biopsy:

    ①   Diffuse effacement of lymph node architecture

    ②   Sheets of pleomorphic lymphocytes

    ③   4–5 times the size of small lymphocytes

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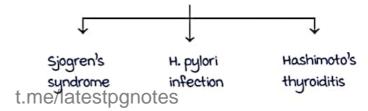
- markers: CD19+, CD 20+,

    BCL-6+

    Surface Ig+

- Highly aggressive with poor prognosis

Active space

- Variants: DLBCL

↓ Primary effusion lymphoma

- Associated with HHr-8, HIV+
- Pleural/ ascitic effusions

↓ Immuno deficiency associated large B cell lymphoma

- Associated with immune deficiency as in HIV+ or following bone marrow transplant

Marginal zone lymphoma   00::45:30

- When it arises at MALT (mucosa associated lymphoid tissue) it is also called as maltoma.
- Usually arises from sites of chronic inflammation

↓ Sjogren's syndrome

↓ H. pylori infection

↓ Hashimoto's thyroiditis

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- Can be associated with t (11:18)
- Tumor marker : CD43+

Hairy cell leukemia   00:45:30

- B cell disorder characterized by hairy cells or hair like projections which is best seen under phase contrast microscope
- Clinically :
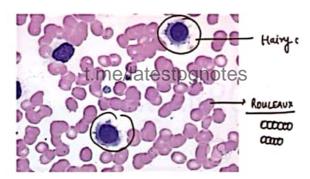
    massive splenomegaly

    Pancytopenia

    Increased risk of atypical mycobacterial infections

Active space

- Pathogenesis:
  - 90% of patients have **BRAFV600E** mutation

    i.e. at 600th position valine is replaced by glutamine

    → Conditions with BRAFV600E mutation
      - ① HCL
      - ② Langerhan cell histiocytosis
      - ③ Papillary carcinoma of thyroid
      - ④ Pilocytic astrocytoma

- Lab diagnosis:-
  - CBC → Hb

    TLC

    Platelets

    } **Decreased (myelofibrosis)**

  - Peripheral smear →

Hairy c
Rouleaux

  - Bone marrow aspirate → **dry tap**

  - Bone marrow biopsy → honeycomb/fried egg appearance

    (also seen in oligodendroglioma)

  - Special stains → **TRAP +** (Tartrate resistant acid phosphate)

  - markers → CD25, CD11C, CD103, DBA44
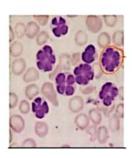
    most specific marker — **ANNEXIN A1**

    (annexin V – apoptotic cells)

Active space
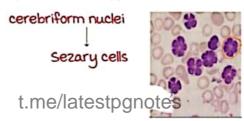
Peripheral T cell disorders   00:54:00

① Adult T cell Leukemia/Lymphoma

- Caused by HTLV-I (Human T cell leukemia virus)

- Flower cells/clover leaf cell
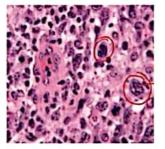
② mycosis fungoides / sezary syndrome

- Cutaneous T cell lymphoma

- Epidermis and upper dermis are infiltrated by cells with

cerebriform nuclei
↓
Sezary cells

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③ Anaplastic large T cell lymphoma (ALCL)

- Pathogenesis : ALK gene mutation on chromosome 2p

    (ALK gene mutation seen in ALCL, Lung adeno-

    carcinoma, inflammatory myofibroblastic

    tumors)

- microscopy: cells with reniform nuclei, voluminous cytoplasm.

Known as hallmark cells

Active space
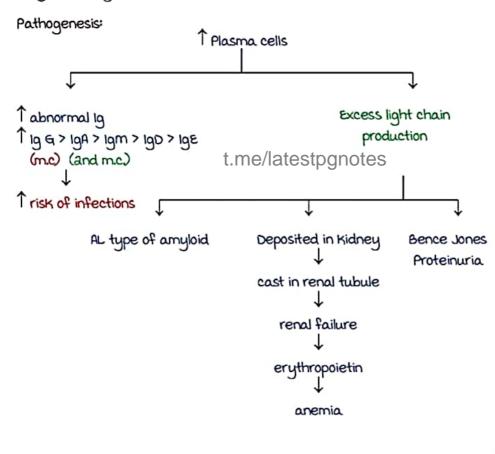
PLASMA CELL DISORDERS
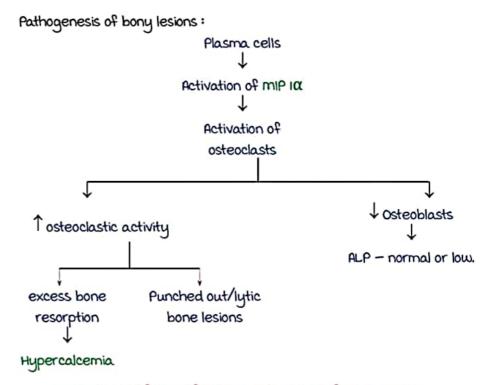
- Abnormal excess Immunoglobulin (Ig) production
- Includes – multiple myeloma
            Plasma cell leukemia
            Smoldering myeloma
            monoclonal gammopathy of undetermined significance
            Waldenstorm's macroglobulinemia

Multiple myeloma (MM) – pathogenesis   00:01:43

- Production of abnormal and excess plasma cells.
- Age: 60-70 years

Pathogenesis:

↑ Plasma cells

↑ abnormal Ig
↑ Ig G > IgA > Igm > IgD > IgE
  (m.c) (and m.c.)
  ↓
↑ risk of infections

Excess light chain production

AL type of amyloid

Deposited in Kidney
↓
cast in renal tubule
↓
renal failure
↓
erythropoietin
↓
anemia

Bence Jones Proteinuria

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Active space

Pathogenesis of bony lesions :

Plasma cells
↓
Activation of MIP 1α
↓
Activation of
osteoclasts

↑ osteoclastic activity

↓ Osteoblasts
↓
ALP — normal or low.

excess bone resorption

Punched out/lytic bone lesions

↓

Hypercalcemia

IL-6: required for proliferation and survival of plasma cells.

Multiple myeloma-clinical features and diagnostic criteria 00:09:23

clinical features

- Pallor, fatigue
- ↑ Infections (m.c cause of death in in multiple myeloma)
- Bone pains, pathological fractures
  - Axial skeleton
  m.c bone affected vertebrae (lumbar)
  skull
  pelvis
- Renal failure → due to IgD deposition

  Cytogenetics : t (11, 14)
              [also in mantle cell lymphoma]

  m.c. gene affected in multiple myeloma: Cyclin D1

Diagnostic criteria (WHO):

  Bone marrow plasma cells > 10%
              or
  Biopsy proven plasmacytoma
              and
  one or more of the following
  myeloma defining events.

Active space

Endorgan damage (crab – lesions)
C Hypercalcemia (S Ca²⁺ > 11 mg/dl)
R Renal abnormalities (S Cr. >2mg %)
A Anemia (Hb < 10 gm/dl)
B Bony lesions
(any lytic or punched out lesions)

Any of the following
biomarkers of malignancy
↓
(Slim features)
S → > 60% plasma cells in
      bone marrow
Li → Involved to uninvolved
      light chain ratio > 100
m → ≥ 1 focal lesion (≥5
      mm) detected by MRI

Lab diagnosis of multiple myeloma   00:17:15

lab diagnosis:

Hb ↓

TLC, platelet → Ⓝ

S. Ca²⁺ : ↑ (metastatic calcification ⊕)

Kidney function test – Abnormal.

X-ray skull:
Lytic/punched out defects

S. Albumin/Globulin ratio : Reversal.

S. β2 macroglobulin ↑

Bence Jones proteinuria:
- light chains of Igs. precipitate at 40–60°C
      ↓
Precipitate disappears on boiling to 100°C
      ↓
Reappear on cooling
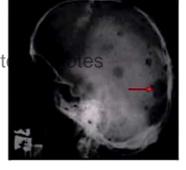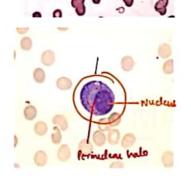
Peripheral smear: Rouleaux
(↑ m protein : RBC stick to each other)
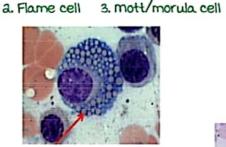
1. Bone marrow aspirate
   ↑ plasma cells.
1. Plasma cell:
• Oval cell
• eccentric nucleus
• perinuclear halo/hoff
• cart wheel chromatin

Nucleus

Perinuclear halo

Active space
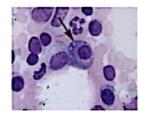
2. Flame cell   3. mott/morula cell   4. Russel body   5. Dutcher body

↓   ↓
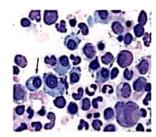
Intra – cytoplasmic   Intra –
inclusion   nuclear
                      inclusion

II. S. Electrophoresis
     m – band (monoclonal Ig band)
                ↓
     due to ↑ S. IgG > 3 gm/dl
III: Immunophenotyping (IPT)
     CD38 +
     Syndecan I +

Other plasma cell disorders   00:30:22

Plasma cell leukemia

>20% plasma cells in peripheral blood

monoclonal gammopathy of undetermined significance (MGUS)
• M.C plasma cell disorder

Bone marrow plasma cells < 10%
No myeloma defining events
S. IgG < 3 gm/dl
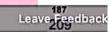
Smoldering/Asymptomatic myeloma
1. S. monoclonal m protein > 3gm/dl
2. BM plasma cells > 10%
3. No CRAB lesions
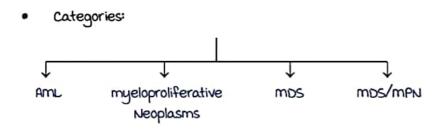
Waldenstorm's macroglobulinemia
1. a/k/a hyper viscosity syndrome
2. ↑ Igm (high molecular weight)
3. Can lead to lymphoplasmacytic lymphoma
      most cases due to MYD 88 mutations

Active space

MYELOID DISORDERS

- Categories:

AML   myeloproliferative   MDS   MDS/MPN
Neoplasms

Myeloproliferative neoplasms   00: 00: 55

1. Panmyelosis
2. Mutation in Tyrosine Kinase or any other growth signalling
   pathway
   ↓
   Growth factor independence
3. Extramedullary hematopoiesis
4. ↑ Risk of transformation to acute leukemia
   [Least with Essential Thrombocytosis (ET)]
5. Later phase → myelofibrosis
   (Spent phase)   ↓
       pancytopenia
   t.me/latestpgnotes
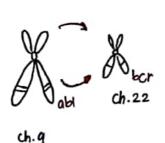
- Diseases: → CML
            → PCV
            → Essential thrombocytosis
            → myelofibrosis.

Chronic myeloid leukemia   00: 04:31

- Age: elderly
- clinically: massive splenomegaly, Hepatosplenomegaly
- Pathogenesis:
  t (9: 22)
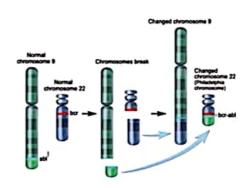
→ BCR-ABL fusion transcript
(210 KDa)
↓
constitutive activation of
Tyrosine Kinase
↓
myeloproliferation
↓
CML

ch.9   abl   bcr   Ch.22

Active space
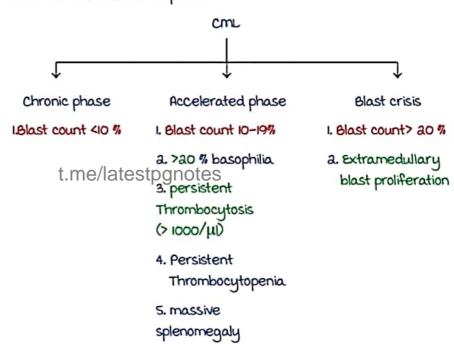
- Changed chromosome 22 → Philadelphia chromosome
- Treatment:

  Tyrosine Kinase inhibitor → Imatinib mesylate
- CML occurs in different phases:

CML

Chronic phase	Accelerated phase	Blast crisis
1.Blast count <10 %	1. Blast count 10-19%	1. Blast count> 20 %
	2. >20 % basophilia	2. Extramedullary blast proliferation
	3. persistent Thrombocytosis (> 1000/µl)	
	4. Persistent Thrombocytopenia	
	5. massive splenomegaly	

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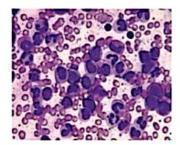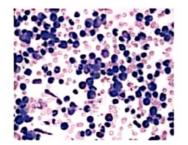
Lab diagnosis of CML   00:12:07

→ Hb: Normal

→ TLC: ↑ ↑ ↑

→ Platelet count: ↑ ↑

→ Peripheral smear: → ↑ no. of all myeloid lineage cells
   → Starts looking like a bone marrow
   → College girl / Garden party appearance
   → Basophilia

Active space
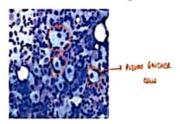
College Girl / Garden party appearance

→ Bone marrow Aspiration: 1. Hypercellular Bone marrow

2. ↑ myeloid: Erythroid ratio

3. Pseudo-Gaucher cells

4. Sea-blue histiocytes

→ Pseudo Gaucher cell
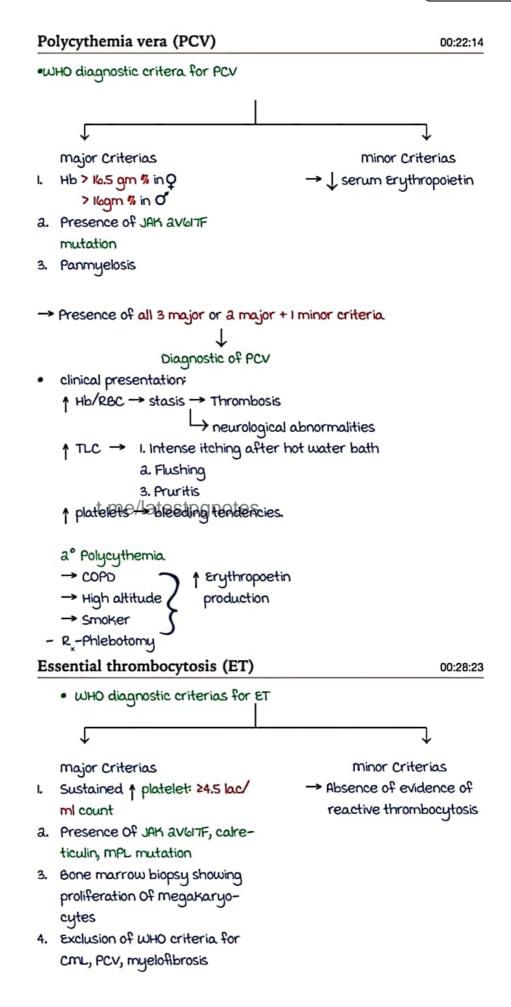
→ NAP (Neutrophil Alkaline Phosphatase) score or LAP (Leukocyte Alkaline phosphatase) score :

• Normal NAP score: 40 –100

• In CML:- NAP score ↓ (except in blast crisis & sometimes in accelerated phase)

↑ NAP score	↓ NAP Score
1. Infections	1. CML
2. Leukemoid reactions	2. Paroxysmal nocturnal Hemoglobinuria (PNH)
3. Stress	
4. Pregnancy	3. myelodysplastic syndrome (MDS)
5. myeloproliferative diseases Other than CML	

• IOC: FISH (Fluorescence Insitu Hybridisation analysis)

↓

t (9:22)

Active space

Polycythemia vera (PCV)   00:22:14

• WHO diagnostic critera for PCV

major Criterias	**minor Criterias**

major Criterias
1. Hb > 16.5 gm % in ♀
   > 16 gm % in ♂
2. Presence of ↑ JAK 2V617F mutation
3. Panmyelosis

minor Criterias
→ ↓ serum Erythropoietin

→ Presence of all 3 major or 2 major + 1 minor criteria
          ↓
      Diagnostic of PCV

• clinical presentation:
   ↑ Hb/RBC → stasis → Thrombosis
                    ↳ neurological abnormalities
   ↑ TLC → 1. Intense itching after hot water bath
            2. Flushing
            3. Pruritis
   ↑ platelets → bleeding tendencies.

   2° Polycythemia
   → COPD   ⎫
   → High altitude ⎬ ↑ Erythropoetin
   → Smoker   ⎭   production
   - R$_x$-Phlebotomy

Essential thrombocytosis (ET)   00:28:23

• WHO diagnostic criterias for ET

major Criterias
1. Sustained ↑ platelet: ≥4.5 lac/ml count
2. Presence Of JAK 2V617F, calreticulin, MPL mutation
3. Bone marrow biopsy showing proliferation Of megakaryocytes
4. Exclusion of WHO criteria for CML, PCV, myelofibrosis

minor Criterias
→ Absence of evidence of reactive thrombocytosis

Active space

→ presence of all 4 major or 3 major+ 1 minor criteria
↓
Diagnostic of ET

• clinical presentation
→ Erythromelalgia
↑↑ platelet count → Clog the small arteries of hands and feets
↓
Throbbing pain in Digits

→ paraesthesia
→ Transient Ischemic attacks

Myelofibrosis   00:32:40

WHO diagnostic criterias

major Criterias
1. Atypical
   megakaryocytic
   hyperplasia
2. Presence of JAK2V617F,
   mPL, calreticulin
3. Exclusion of criterias
   for other myeloprolif-
   erative neoplasms

minor Criterias
→ ↓LDH
→ Anemia
→ Splenomegaly
→ Leukoerythroblastic
   blood picture

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→ Presence of all 3 major or 2 major + at least 1 minor criteria
↓
Diagnostic for myelofibrosis
• Clinical presentation : massive splenomegaly
• Pathogenesis : megakaryocytic hyperplasia
↓
↑PDGF
↓
fibrogenic → Bone marrow fibrosis

• Lab diagnosis :
→ HB
→ TLC   } ↓ (Pancytopenia)
→ Platetet count
→ Peripheral smear :

→ BONE
→ FIBROUS

RBCs go through this → change in shape

Active space

Dacrocytes / Tear drop cells

+

Leukoerythroblastic blood picture
→ Presence of immature red cells+ white
cell precursors in peripheral blood

- Leukoerythroblastic blood picture seen in:
→ myelofibrosis
→ space occupying lesion of bone marrow like
  metastatic cancer ₹ granuloma
- Bone marrow Aspiration → Dry Tap
- Bone marrow biopsy → ↑ Fibrosis
                            Reticulin Stain (silver)
                       → Abnormal megakaryocytes
                            ↓
                    cloud like appearance

Myelodysplastic syndrome (MDS)   00:43:41

- Clonal stem cell disorders
  → characterised by
                        ↓
cytopenias   ↑ risk of   dysplasia in
              transformation to erythroid,
              AML   myeloid,
                                 megakaryocytic
                                 lineages.

- Types
                    MDS

Primary   secondary (therapy
                                  related)

- m.c cytogenetic abnormality in adult MDS

  ↓

  del5q

- m.c cytogenetic abnormality in children MDS

  ↓

  monosomy 7

-

<p align="center">Dysplasia</p>

Erythroid	myeloid	megakaryocytic
1. megaloblastoid change	1. Toxic Granules	1. Pawn Ball megakaryocyte (multiple separate nuclei)
2. Nuclear budding	2. Dohle bodies	2. micromega-karyocyte
3. Nuclear bridging	3. Pseudo Pelger-Huet cell	3. megakaryocyte with single lobe
4. Ringed sideroblasts		

→ Budding

→ Toxic granules

Nuclear Bridge

DOHLE BODY

→Ringed sideroblasts

→ PSEUDO PELGER HUET

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Warning : Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with Marrow Edition 4 videos.

MDS/MPN and LCH   00:52:15
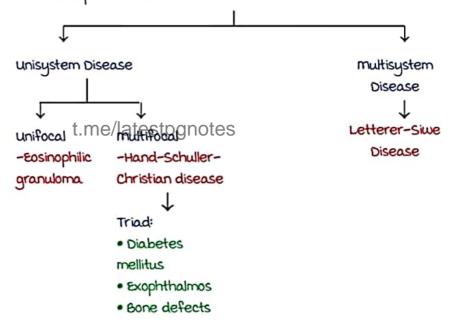
MDS/MPN

- Combination of myelodysplastic syndrome and myeloproliferative neoplasm

Active space

categories

Chronic myelo-monocytic lecukemia (CmmL)	Juvenile myelo-monocytic lecukemia (JmmL)	Atypical CmL (aCmL)
→ Blast count <20%	→ CmmL criteria present	→ Philadelphia chromosome ⊖
→ monocytes >1000/ cu mm	→ HB F ↑↑↑	→ Poor prognosis
→ BCR-ABL negative	→ monosomy 7	

Langerhans cell histiocytosis (LCH)
- Proliferation of immature dendritic cells
- Pathogenesis : 50-60% → BRAF V600 E
- clinical presentation :

Unisystem Disease	multisystem Disease
	↓
	Letterer-Siwe Disease

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Unisystem Disease branches:

Unifocal
-Eosinophilic granuloma

multifocal
-Hand-Schuller-Christian disease
↓
Triad:
- Diabetes mellitus
- Exophthalmos
- Bone defects

- Biopsy : Cell with nuclear grooves
  ↓
  Coffee bean appearance
- Disorders with longitudinal grooves on H & E :
1. LCH
2. Papillary cancer of thyroid
3. Brenner's tumour
4. chondroblastoma
5. Granulosa cell tumour
- Electron microscopy : Birbeck granules
  tennis racquet appearance
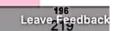
Active space

- Immunohistochemical markers :
→ Langerin
→ CDIA
→ S-100
→ CD 207 : most important marker
→ HLA-DR

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Active space

BLOOD GROUPING AND TRANSFUSION MEDICINE

Blood groups   00:01:15

- major → A, B, O

- minor → Kell, Duffy, Kidd, MNS

*ABO blood group system shows the property of Codominance

ABO	RH
1. Gene on chromosome 9	Gene on chromosome 9
2. A, B, AB & O	+/-
3. seen on semen, sweat, saliva	not seen
4. IgM naturally occuring antibody	IgG, does not occur naturally

Blood group	Antigen	Antibody
O	H	Anti A, Anti B
A	A	Anti B
B	B	Anti A
AB	A, B	No Antibody

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* VWF and factor VIII are 25% lower in healthy group O individuals

* Bombay blood group: Rate blood group with the following antibodies
       – anti A, and B and anti H

- Patients with Bombay blood group cannot be transfused with blood groups A, B or O.
- They can receive blood only from a Bombay blood group

Active space

Blood transfusion

- Blood bag: Volume → 350ml/ 450 ml (for components)

- Anticoagulants in a blood bag

ACD	CPD	CPD - A	SAGM
Acid Citrate Dextrose	Citrate Phosphate Dextrose	CPD + Adenine	Sodium Adenine Glucose mannitol
Shelf life 21 days	Shelf life 21 days	Shelf life 35 days	Shelf life 42 days
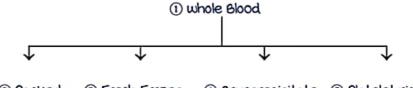
C → Citrate → anticoagulant
P → Phosphate → buffer to maintain pH
D → Dextrose → provides nutrition
A → Adenine → substrate for ATP synthesis

- Blood is screened for following disease before transfusion
  1. Hep B
  2. Hep C → most common transfusion transmitted Infection.
  3. malaria
  4. Syphilis
  5. HIV

Blood components

① whole Blood

② Packed RBCs   ③ Fresh Frozen Plasma (FFP)   ④ Cryoprecipitate   ⑤ Platelet rich Plasma (PRP)

* Components should be separated within 4 hours of blood collection.

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Blood product	Volume	Storage temp	Shelf life	use
Packed RBCs	350ml	2 – 6°C	CPD– 21 d CPD–A– 36d SAGM – 42d	Severe anemia 1 unit– ↑ Hb by 1g%.
whole blood	350ml	2 – 6°C	similar to Packed RBCs	Acute blood loss
Fresh frozen plasma	200ml	– 18°C or lower	1 year	multiple coagulation factor deficiency
cryoprecipitate [Factor VII Factor XIII Fibrinogen VWF]	10 – 20ml	– 18°C or lower	1 year	– Hemophilia A – VWD – Hypofibrinogenemia – Factor XIII deficiency
Random donor platelets (RDP)	50 – 70ml	20 – 24°C with agitation	5 days	Thrombocytopenia 1unit – ↑ Platelet by 10, 000/ mm³
Single donor platelet (SDP)	200 – 300ml	20 – 24°C with agitation	5 days	1 unit– ↑ Platelet by 30,000– 50,000/ mm³

* Life span of transfused RBCs → 50 – 60 days
* Infection transmitted by all blood products → malaria
* Blood components most prone to bacterial contamination → Platelets

Transfusion protocols   00:27:54

1. Transfusion should commence within 30 minutes of taking out of fridge

2. Should be completed within 4 hours

3. Size of micropore filter is 170 microns

4. Size of needle used 18 – 19G

Active space

Transfusion reactions   00:29:48

```
                        Transfusion reactions
             ┌───────────────────┴───────────────────┐
             ↓                                         ↓
      Immediate reactions                       Delayed reactions
```

Immediate reactions	Delayed reactions
- Febrile hemolytic blood transfusion reaction	- Delayed hemolytic transfusion reactions.
- Febrile nonhemolytic blood transfusion reaction (most common)	- Post transfusion purpura
- Allergies	- Graft versus host disease
- TRALI (Transfusion related acute lung injury)	- Infections

Massive blood transfusion (MBT)   00:31:53

- Definition: Transfusion of patients whole blood volume within 24 hours
- Ratio of RBC: FFP: Platelets ⟹ 1:1:1
- Complications:

    C → Coagulopathies (dilutional)

    A → metabolic Alkalosis(mc)

    T → Hypothermia

    C → Citrate toxicity: tingling, numbness

    H → Hyperkalemia → arrhythmia.
         Hypocalcemia

* most common cause of death after MBT → coagulopathies → DIC

Transfusion related acute lung injury   00:36:15

- Transfusion Related Acute Lung Injury
- Definition: Development of respiratory symptoms within 6 hours of blood transfusion
- Clinical features: dyspnoea, tachypnoea, fever

Active space

- Differential diagnosis: ARDS – Acute respiratory distress syndrome

   (X – ray – Bilateral white out appearance in both)

- Pathogenesis: Not completely understood,

   Antibody mediated with antibodies against

   HLA II   Human
                 neutrophilic
                 antigen

- more common with FFP transfusion

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Active space

HEMOSTASIS

Hemostasis - introduction   00:00:17

- Important factors for hemostasis

| Vascular | platelets | Coagulation |

Endothelial injury
↓
Vaso constriction
↓
Formation of Primary hemostatic plug
↓
Clot

Primary and secondary haemostasis   00:02:12

Primary haemostasis:
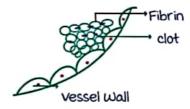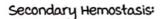
1) platelet adhesion:
   ↓
   between Von Willebrand factor
   and gp Ib - Ix shape change.
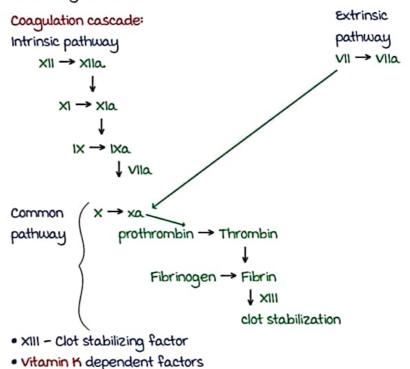
2) Platelet aggregation:
   - by an interaction between
     gp IIb - IIIa

→ clot gets stable
   after fibrin deposition

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Secondary Hemostasis:

Coagulation cascade:
Intrinsic pathway

$XII \rightarrow XIIa$

$\downarrow$

$XI \rightarrow XIa$

$\downarrow$

$IX \rightarrow IXa$

$\downarrow VIIa$

Extrinsic pathway

$VII \rightarrow VIIa$

Common pathway

$X \rightarrow Xa$

prothrombin $\rightarrow$ Thrombin

$\downarrow$

Fibrinogen $\rightarrow$ Fibrin

$\downarrow XIII$

clot stabilization

- XIII – Clot stabilizing factor
- Vitamin K dependent factors

factor 2, 7, 9, 10, Protein c, Protein S.

Tests in hemostasis   00:11:28

1) Platelet count (PLC)

Normal – 1.5 – 4 lakhs / cumm

decrease in platelet: Thrombocytopenia

$\downarrow$ production $\downarrow$ destruction

Bone marrow suppression   ITP
   eg : Aplastic anemia

2) Bleeding time (BT)

Normal : 2– 8 mins.

$\rightarrow$ Increase in BT :

$\downarrow$ platelet count   Functional defect of platelets

3) Prothrombin Time (PT)

- Test for extrinsic pathway of coagulation
- Normal : 11 – 14 sec .
- $\uparrow$ PT – VII deficiency.

4) Activated Partial thromboplastin time (APTT)

– Nomal – 30 – 34 sec,

– Test for intrinsic pathway of coagulation

– XII, X, IX, VIII factors

↓

Decrease

↓

aPTT

– Factor X deficiency, prothrombin, fibrinogen– PT, aPTT

Protocols for coagulation studies   00:17:56

1) Always take the sample in plastic syringe.

2) platelet poor plasma for coagulation study.

3) Anti – coagulant used – 3. 2 %. Trisodium citrate.
   → green coloured cap.
   Vials
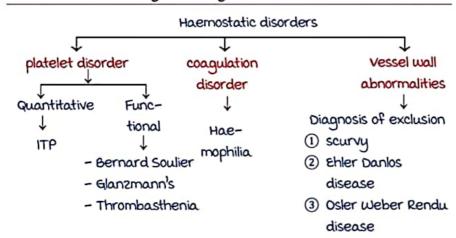
4) within 2hrs of blood collection– coagulation test has to be done

5) Sample is stored at room temperature.

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Disorders of bleeding and coagulation   00:21:32

Haemostatic disorders

platelet disorder   coagulation disorder   Vessel wall abnormalities

Quantitative   Func-   Diagnosis of exclusion
↓   tional   ↓   ① scurvy
ITP   ↓   Hae-   ② Ehler Danlos
                – Bernard Soulier   mophilia   disease
                – Glanzmann's   ③ Osler Weber Rendu
                – Thrombasthenia   disease

Difference between bleeding and coagulation disorders   00:25:03

Bleeding disorder	coagulation disorder
I. Autosomal	I. X – linked
m = F	m >>> F
2. Clinically:	2. Clinically:

Active space

- petechiae
- purpura
- mucosal bleeds
- prolonged bleeding after
  any injury

- Haemarthrosis
- ecchymosis

3. lab tests:

PLC ⎤
BT   ⎬ can be affected
PT   ⎭
aPTT ⎱ normal

3. PTC ⎫
   BT ⎬ can be normal

PT   ⎫
aPTT ⎬ can be affected
     depending on
     coagulation
     factor deficiency

4. eg: ITP

4. eg : Haemophilia

- Von Willebrand's disease ⎱ have both bleeding
              DIC   ⎰ and coagulation defect

Immune thrombocytopenic purpura (ITP)   00:29:02

Type II hypersensitivity reaction.

caused by anti-platelet antibodies.

Acute	chronic
① < 6 months	> 6 months
② Sudden onset	insidious onset
③ usually children	Adolescents (adults)
④ Preceding history of viral infection	No such history
⑤ Platelet count ↓↓↓ (markedly reduced)	Platelet count that ↓↓ (moderately reduced)
⑥ Self limiting	requires Rx: Steroids immunosuppressants

Clinical presentation:

- Petechiae, purpura, mucosal bleeds, gum bleeding.

Active space

Lab test:

→ PLC ↓↓↓

   BT

   PT
   APTT } Normal

→ + ve Coomb's Test

- Bone marrow aspiration (BMA) : megakaryocytic hyperplasia
                             no of megakaryocyte.

Bernard Soulier syndrome and Glanzmann's thrombasthenia

00:36:12

1) Bernard Soulier syndrome
- Deficiency of gp Ib – IX or defect in platelet adhesion
- lab tests: PLC – Normal
      BT – increased
      PT
      aPTT } Normal
- Peripheral Smear (P/S)– Giant platelets.
- Platelet aggregation with ristocetin– abnormal
  ADP, collagen – normal.
             ↓
Using Platelet aggregatometer.
Ristocetin:
      ↓
Chemical: helps in activation/interaction of
          "VWF with gpIb – IX"
2) Glanzmann' s thrombasthenia
- X linked recessive disease.
- m > > F
- Pathogenesis:
    → deficiency of gpIIb– IIIa
    → defect in platelet aggregation
- lab test:
    → BT –increased
    → platelet aggregation with ristocetin – normal
    → platelet aggregation with ADP, Collagen – abnormal
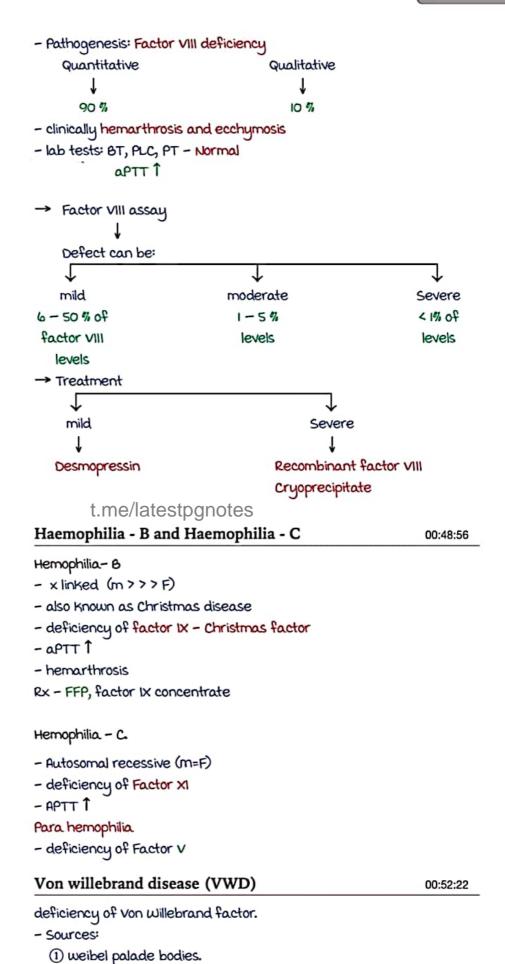
Haemophilia - A

00:43:10

- X linked recessive disorder.
- m>>>F
- Factor VIII Synthesis   → liver
                          → Kidney

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- Pathogenesis: Factor VIII deficiency

Quantitative	Qualitative
↓	↓
90 %	10 %

- clinically hemarthrosis and ecchymosis
- lab tests: BT, PLC, PT – Normal
  aPTT ↑

→ Factor VIII assay
        ↓
   Defect can be:

mild	moderate	Severe
↓	↓	↓
6 – 50 % of	1 – 5 %	< 1% of
factor VIII	levels	levels
levels		

→ Treatment

mild	Severe
↓	↓
Desmopressin	Recombinant factor VIII
	Cryoprecipitate

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Haemophilia - B and Haemophilia - C   00:48:56

Hemophilia- B
- x linked (m > > > F)
- also known as Christmas disease
- deficiency of factor IX – Christmas factor
- aPTT ↑
- hemarthrosis
Rx – FFP, factor IX concentrate

Hemophilia – C.

- Autosomal recessive (m=F)
- deficiency of Factor XI
- APTT ↑
Para hemophilia
- deficiency of Factor V

Von willebrand disease (VWD)   00:52:22

deficiency of von Willebrand factor.
- Sources:
  ① weibel palade bodies.

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② Endothelial cells.
③ megakaryocytes
④ liver
- mc inherited bleeding disorder
- a/k/a Pseudo hemophilia.
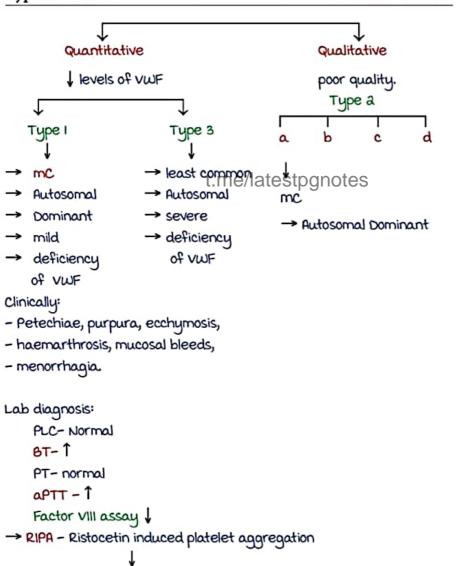
Functions VWF:
① platelet adhesion to endothelium (gp Ib – Ix)
② Carrier for factor VIII (Stabilizes)
- VWF + factor VIII —t 1/2 " 12hr
  Factor VIII alone – t 1/2= 24hr
- Both coagulation and bleeding defect seen.
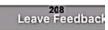
Types of VWD   00:56:38

```
              Quantitative                    Qualitative
            ↓ levels of VWF                   poor quality.
                                                 Type 2
       Type I            Type 3          ┌──────┬──────┬──────┐
         ↓                 ↓             a      b      c      d
    → mC            → least common       ↓
    → Autosomal     → Autosomal          mc
    → Dominant      → severe
    → mild          → deficiency         → Autosomal Dominant
    → deficiency       of VWF
       of VWF
```

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Clinically:
- Petechiae, purpura, ecchymosis,
- haemarthrosis, mucosal bleeds,
- menorrhagia.

Lab diagnosis:
    PLC- Normal
    BT- ↑
    PT- normal
    aPTT - ↑
    Factor VIII assay ↓
→ RIPA – Ristocetin induced platelet aggregation
                    ↓
                prolonged.

Active space

Disseminated intravascular coagulation   01:01:31

→ DIC aka- Consumption coagulopathy.
→ Causes
  - Pregnancy complication:
    - septic abortion
    - amniotic fluid embolism
  - Severe toxemia
  - Severe meningococcemias
  - Burns
  - Cancers - AmL -m3 (acute promyelocytic leukemia)
          - cancer colon, Pancreas, rectum.

Pathogenesis: Endothelial Injury.

Coagulation cascade   Fibrinolytic cascade

        ↓
    Thrombin   →   Bleeding

Consumption of (diagram of blood vessel) → Blood clot
        ↓   RBC get destroyed - Schistocytes
coagulation factors → Consumption coagulopathy

Clinically - massive bleeding.
lab test: t.me/latestpgnotes
→ P. smear - Schistocytes / helmet cells
        - Fragmented red cells (cell shapes)
→ PLC - ↓
   BT -
   PT   }
   aPTT {

→ Fibrin degradation products (FDPs) -
   break down of fibrin produce - D- Dimers. ↑
                    ↓
          most specific test for DIC.

Rx: _ Treat the cause
  - FFP

High yield table

01:09:16

Disorder	PLC	BT	PT	APTT	Extra
Bernard Soulier	N	↑	N	N	① Platelet aggregate with Risto-cetin is abnormal ② Giant platelets
Glanzmann's Thrombasthenia	N	↑	N	N	① Platelet aggregation with ADP ② Collagen abnormality
ITP	↓	↑	N	N	BMA megakaryocyte
TTP	↓	↑	N	N	Schistocytes
HUS	↓	↑	N	N	reticulocyte
Hemophilia-A	N	N	N	↑	Factor VIII
Hemophilia - B	N	N	N	↑	Factor IX
VWD	N	↑	N	↑	RIPA- abnormal
DIC	↓	↑	↑	↑	D- Dimer
Vitamin K deficiency	N	N	↑	↑	
Vascular disorder	N	N	N	N	

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Active space

PRACTICAL HEMATOLOGY

Bone marrow examination   00:00:58

- Bone marrow needle
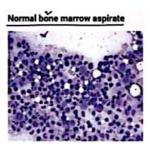
- Bone marrow needle ⟨ Aspiration / Biopsy

- Needles used :
  - Salah's needle ⎫ Bone marrow aspiration
  - Klima needle ⎭
  - t.me/latestpgnotes
  - Jamshidi needle → Bone marrow biopsy .
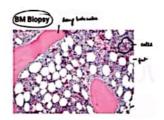
- Site : iliac crest, PSIS - posterior superior iliac spine, sternum

- Dry tap :
  - Dry tap on bone marrow aspirate → Bone marrow biopsy
  - Causes :   Aplastic anemia
    - myelofibrosis
    - Hairy cell leukemia
    - myelophthisic anemia

- Normal bone marrow aspirate

Normal bone marrow aspirate

- Normal bone marrow biopsy
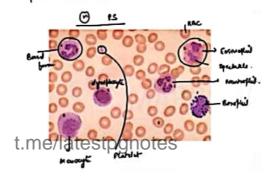
% cellularity on BM = 100 - Age
eg: if patient age = 30y
   % cellularity = 100-30
              = 70 %
⇒ 70% cells, 30% fat
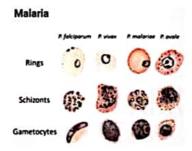
Peripheral smear   00:06:53

Normal Peripheral smear.

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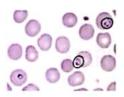
- Components :
    - RBCs
    - Platelets
    - Band forms : precursor of neutrophil
    - Monocytes : Kidney shaped, non-granular nucleus
    - Lymphocyte : small cell, non-granular cytoplasm and nucleus
    - Eosinophil : brick red granules, spectacle nucleus
    - Basophil : dark bluish granules, obscured nucleus
    - Neutrophil

- Peripheral Smear of Malaria

Malaria
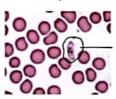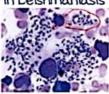
- Important forms :

  • Ring form of P. Falciparum and P. vivax

  • Gametocyte of P. Falciparum

★ Bone marrow aspirate in Leishmaniasis

- Characteristic finding on aspirate
  ↳ LD Bodies with double dot appearance

Vacutainers   00:10:31

① Red Cap :   Plain vial
                 Uses : enzyme studies, hormonal assays
② Yellow cap :   Gel separator
                 Uses : enhances separation of serum.
                        enzyme studies, hormonal assays
③ Lavender cap : EDTA
                 chelates calcium
                 Uses : Peripheral smears, CBC
                         ESR determination by Wintrobe's
                         method
④ Green cap :   Heparin
                 Uses : Osmotic fragility
                         Immunophenotyping, ABG.

⑤ Pink cap :   EDTA

      uses : In blood banks for cross-matching

⑥ Blue cap :   Citrate

      Chelates calcium

      uses : ESR determination by Westergren's method.

      Coagulation studies.

⑦ Grey cap :   NaF – Sodium fluoride

      inhibits enolase → inhibits glycolysis

      use : blood sugar estimation.

Instruments   00:17:40

- Sahli's haemoglobinometer

SAHLI'S HAEMOGLOBINOMETER
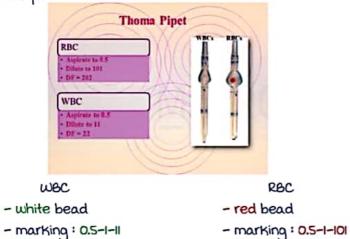
-   Use : To measure Hb levels
-   Principle : Hb is converted to acid hematin by the addition of O.IN HCL.

- Improved Neubauer's Chamber

Neubauer's chamber

☐ areas of the grid where WBC are counted

☐ areas of the grid where RBC are counted

-   WBC count = N x 50 / cumm

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- RBC count = N × 10,000 / cumm
- Thoma Pipet

Thoma Pipet

RBC
• Aspirate to 0.5
• Dilute to 101
• DF = 202

WBC
• Aspirate to 0.5
• Dilute to 11
• DF = 22

WBC
- white bead
- marking : 0.5-1-11

RBC
- red bead
- marking : 0.5-1-101
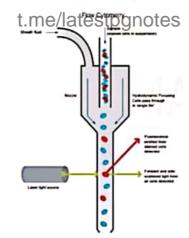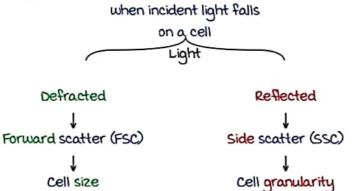
Flow cytometry   00:20:55

Flow cytometry

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- Principle :

```
            when incident light falls
                 on a cell
                   Light

      Defracted              Reflected
          ↓                      ↓
   Forward scatter (FSC)   Side scatter (SSC)
          ↓                      ↓
      Cell size            Cell granularity
```

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Flow cytometry
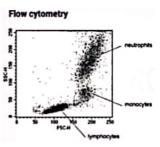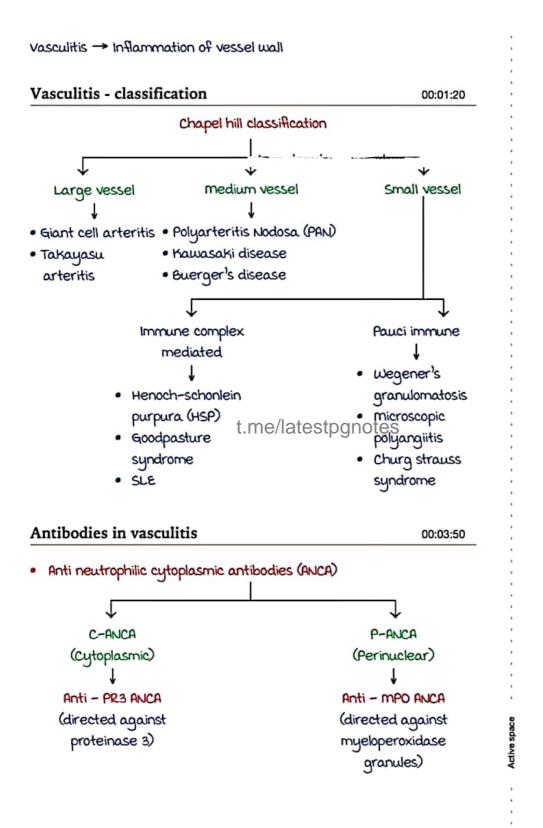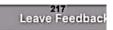
- monocytes :   high FSC
                     low SSC

- Neutrophils :   high FSC
                     high SSC (because of granules)

- Lymphocytes :   low FSC
                     low SSC

- In AML, myeloblasts : high FSC
                        high SSC

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BLOOD VESSELS - VASCULITIS

Vasculitis → Inflammation of vessel wall

Vasculitis - classification   00:01:20

Chapel hill classification

Large vessel	medium vessel	Small vessel
• Giant cell arteritis	• Polyarteritis Nodosa (PAN)	
• Takayasu arteritis	• Kawasaki disease	
	• Buerger's disease	

Immune complex mediated
- Henoch-schonlein purpura (HSP)
- Goodpasture syndrome
- SLE

Pauci immune
- Wegener's granulomatosis
- microscopic polyangiitis
- Churg strauss syndrome

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Antibodies in vasculitis   00:03:50

- Anti neutrophilic cytoplasmic antibodies (ANCA)

C-ANCA (Cytoplasmic)
→ Anti – PR3 ANCA (directed against proteinase 3)

P-ANCA (Perinuclear)
→ Anti – mPO ANCA (directed against myeloperoxidase granules)

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Three patterns of ANCA

p-ANCA, show a *perinuclear staining* pattern

c-ANCAs, show a *diffusely granular, cytoplasmic staining* pattern

Atypical that develop against *antigens other than MPO or PR3* will occasionally result in *patchy staining*

p-ANCA ⊕ in : • microscopic polyangiitis
                • Churg strauss syndrome

c-ANCA ⊕ in : • Wegener's granulomatosis (c-ANCA > p-ANCA)

Atypical ANCA ⊕ in : • Auto immune Hepatitis
                   • I° Biliary cirrhosis

Auto immune disorders with ⊕ ANCA → • SLE   } usually
                          • Ulcerative colitis } p-ANCA ⊕

• Anti Glomerular basement membrane (GBM) antibody:
   – Seen in Goodpasture's syndrome
• Anti endothelial antibody:
   – ⊕ in Kawasaki disease

Giant cell arteritis   00:10:03
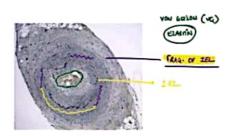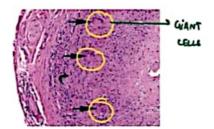
– Large vessels involved
– a/k/a Temporal arteritis
– mc vasculitis in adults / elderly –average age > 50yr.
– mc vessel affected → Superficial temporal artery
– Other vessels → Ophthalmic artery, Vertebral artery
– Clinical features: • Headache (mc symptom)
                    • Jaw pain
                    • Jaw claudication (most specific symptom)
                    • Blindness (Ophthalmic artery involvement)
                       associated with Polymyalgia Rheumatica
                    • ↑ ESR
– Histopathology: Biopsy of involved vessel.
   • Giant cell
   • Granulomatous inflammation
   • Fragmentation of internal elastic lamina

TEMPORAL ARTERITIS

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Takayasu arteritis 00:17:06

- a/k/a Aortic arch syndrome
- mc vessel affected: Subclavian artery
- Least common vessel affected: Coronary artery
- K/a Pulseless disease
- Clinically - Loss of pulse in the upper extremities
- Age → < 40 yr.
- Histopathology: - Intimal thickening → Luminal narrowing
  - Granulomatous inflammation
    +
  Giant cells
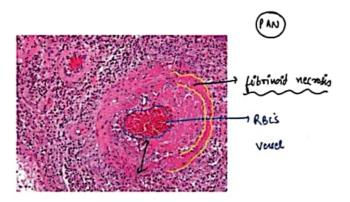
Polyarteritis nodosa (PAN) 00:20:26

- Type III hypersensitivity reaction
  Immune complex mediated vasculitis
- most vessels can be affected except Pulmonary
  "Lung is spared"
- Can involve - Liver, Kidney, heart, GIT
- Kidney can be affected →but Glomerulonephritis not seen
- mCC of death → Renal failure
- mc type of vasculitis which can lead to mono neuritis multiplex
- 30% patients are HBsAg ⊕
- p-ANCA ⊖

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- Histopathology: • Segmental transmural necrotizing inflammation
  → fibrinoid necrosis
  • Inflammatory infiltrates seen in all 3 layers of blood vessel.
- All stages of disease can be seen in a vessel at the same time.

(PAN)

→ fibrinoid necrosis
→ RBCs
Vessel
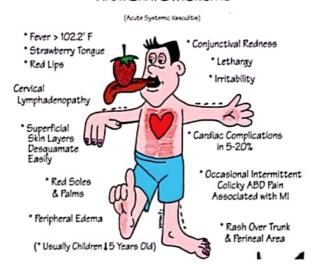
Kawasaki disease   00:27:47

- aka mucocutaneous lymph node syndrome
  K → Conjunctivitis (bilateral - non suppurative)
  A → Age < 4 yrs. (mc vasculitis - causing death in children)
  W → Vasculitis
  A → Adenopathy (cervical)
  S → Strawberry tongue, Skin rash, Swelling
  A → Anti endothelial antibodies
  K → Coronary artery involvement → MI
  I → ↑ platelets.

KAWASAKI SYNDROME

(Acute Systemic Vasculitis)

* Fever > 102.2° F
* Strawberry Tongue
* Red Lips

Cervical
Lymphadenopathy

* Superficial
  Skin Layers
  Desquamate
  Easily

* Red Soles
  & Palms

* Peripheral Edema

(* Usually Children ↓ 5 Years Old)

* Conjunctival Redness
* Lethargy
* Irritability

* Cardiac Complications
  in 5-20%

* Occasional Intermittent
  Colicky ABD Pain
  Associated with MI

* Rash Over Trunk
  & Perineal Area

- Histopathology - Transmural inflammation

Buerger's disease   00:32:37

- middle aged male smokers
- aka Thromboangiitis obliterans
- Associated with HLA B5, A9
- HLA B12 is protective
- Can involve arteries, capillaries, nerves → painful lesions
- Clinically: • Intermittent claudication
                • Rest pain
                • Gangrene
- Histopathology: – Neutrophilic microabscesses
                   – Granulomatous inflammation

Microscopic polyangiitis   00:37:14

- Small vessel vasculitis
- aka leukocytoclastic vasculitis
- p-ANCA ⊕
- Kidney and lung can be affected
- Glomerulonephritis ⊕
- Clinical features: • GIT, Kidney, Skin problems
- Histopathology: • Segmental inflammation (rarely transmural)
                     • No granulomas
                     • All lesions are of same age

Wegener's granulomatosis   00:40:46

- Now k/a Granulomatosis with polyangiitis
- Triad: – Lesions of upper & lower respiratory tract.
              • Sinusitis
              • Otitis media
              • Lung involvement
            – Vasculitis
            – Kidney involvement
              • Focal necrotizing glomerulonephritis
              • Rapidly progressive glomerulonephritis (RPGN)
If only lung involvement ⟹ Limited wegener's granulomatosis
- c-ANCA ⊕ (c-ANCA > p-ANCA) → 95% case
- Histopathology:
  • Granuloma with giant cells

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Churg Strauss syndrome   00:44:08

- aka Allergic granulomatosis with angiitis.
- Associated with Bronchial asthma, Eosinophilia hence allergic.
- Clinically: GIT & skin problems
- p-ANCA ⊕
- mc cause of death → Cardiac failure
- Histopathology: Necrotizing granulomas

Henoch schonlein purpura   00:45:53

- Type III Hypersensitivity reaction
- IgA mediated vasculitis
- Platelet count ⓝ but purpura seen due to vasculitis
- mc vasculitis in children overall
- Clinically: Colicky abdominal pain, arthralgia, kidney disease, non-palpable purpura [mc site buttock]
- Histopathology: IgA deposition in the vessel wall

Behcet's disease   00:48:34

- Small vessel vasculitis
- Can be HLA B5, B-51 associated
- Recurrent oral / genital ulcers, uveitis
- Neutrophilic vasculitis
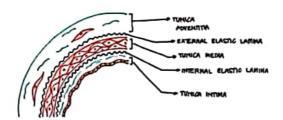
Granulomatous vasculitis: Giant cell, Takayasu, Churg strauss syndrome, Wegener's granulomatosis, Buerger's disease

Active space

BLOOD VESSELS - SCLEROSIS
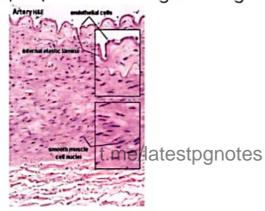
Normal histology of blood vessels   00:02:03
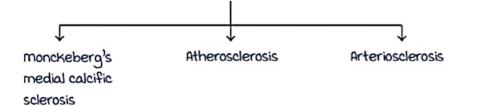
- All blood vessels have 3 layers :
- Tunica intima lined by endothelial cells.

- All vessels except capillaries are lined by these 3 layers :

Sclerosis   00:05:53

monckeberg's   Atherosclerosis   Arteriosclerosis
medial calcific
sclerosis

monckeberg's medial calcific sclerosis :
→ Clinically insignificant
→ Age (>50 yrs)
→ Involves tunica media and internal elastic lamina
→ Dystrophic calcification

Stain for calcium:

    1) Von Kossa

    2) Alizarin red stain

- Calcification appears basophilic   lumen with RBC's

Active space
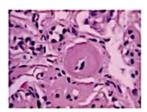
Arteriosclerosis   00:09:17

Thickening or hardening of arteries.

Hyaline
- Seen in patients with benign HTN, DM
- Pink homogenous, glassy appearance of arteriolar wall

Hyaline arteriosclerosis

Hyperplastic
- Seen in patients with malignant HTN.
- Hyperplasia of the wall
  ↓
  Smooth muscle proliferation
- Concentric laminated thickening
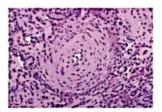
HPE ⊙ ↓
1) onion skin appearance
2) Fibrinoid necrosis

Onion skin appearance

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Onion skins in medicine   00:14:23
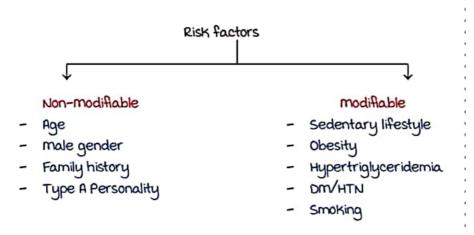
1) HPE of malignant HTN (blood vessel)
2) Nerve biopsy in chronic Inflammatory demyelinating polyneuropathy (onion bulb)
3) Biopsy in primary sclerosing cholangitis.
4) Spleen in SLE.
5) X-ray of Ewing's sarcoma.
6) Electron microscopy of Tay Sachs disease.

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Atherosclerosis   00:16:41

Deposition of an atheromatous plaque in the vessel wall

Risk factors

Non-modifiable
- Age
- Male gender
- Family history
- Type A Personality

Modifiable
- Sedentary lifestyle
- Obesity
- Hypertriglyceridemia
- DM/HTN
- Smoking

Additional risk factors

1) Infections – CMV, chlamydia, Herpes
2) Lipoprotein (A, APO B-100, APO A)
3) Metabolic syndrome.
4) Hyperhomocysteinemia.

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Pathogenesis of atherosclerosis   00:20:07

- Result of endothelial injury.
- Response to injury hypothesis

Risk factors
↓
Vascular endothelial injury
↓
Accumulation of lipoprotein – LDL and its oxidized form
↓
monocyte adhesion.
↓
Smooth muscle migration from tunica media to intima and proliferates.
↓
"Neo – Intimal hyperplasia"
↓
formation of an "Atheromatous Plaque"
→ Earliest lesion – 'Fatty streak'
        1 mm yellowish lesion.
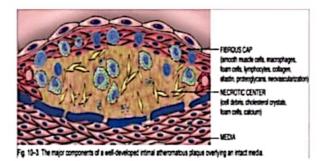
Active space

Atheromatous plaque components and types of plaque and complications

00:24:00

FIBROUS CAP
(smooth muscle cells, macrophages, foam cells, lymphocytes, collagen, elastin, proteoglycans, neovascularization)

NECROTIC CENTER
(cell debris, cholesterol crystals, foam cells, calcium)

MEDIA

Fig 10-3 The major components of a well-developed intimal atheromatous plaque overlying an intact media.

Atheromatous plaque components

Fibrous cap:

- Smooth muscle cells and collagen

Shoulder :
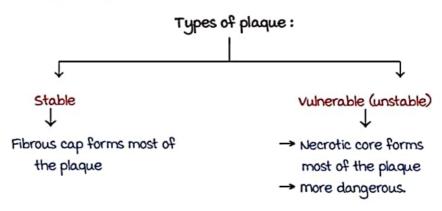
- Cellular area comprising of smooth muscles cells, macrophages and T-lymphocytes.

Necrotic core :

- dead cells

- Lipid laden macrophages

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↓

Foam cells

- Cholesterol clefts.

Types of plaque :

Stable
↓
Fibrous cap forms most of the plaque
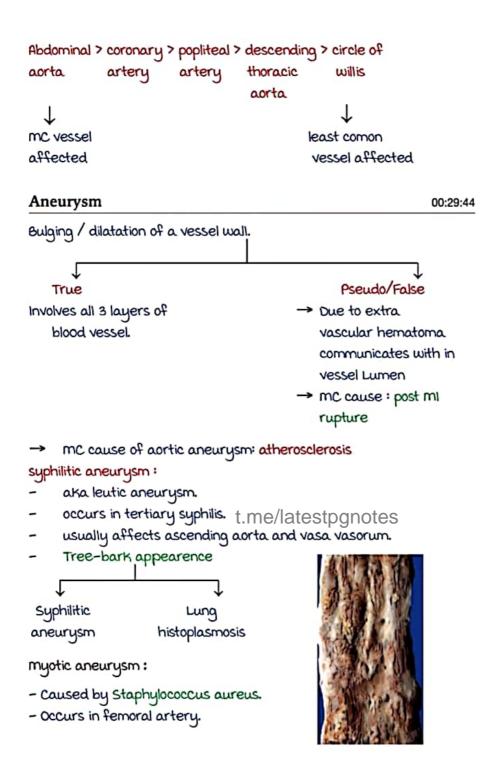
Vulnerable (unstable)
↓
→ Necrotic core forms most of the plaque
→ more dangerous.
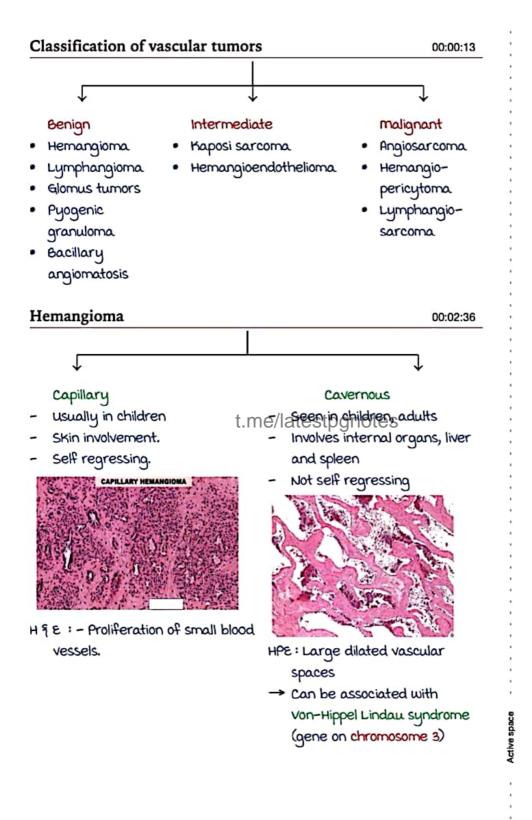
Complications in plaque :

A – Aneurysm
C – Calcification
U – Ulceration
T – Thrombosis
E – Embolism.
→ Vessel affection by atherosclerosis : (Descending order)

Abdominal > coronary > popliteal > descending > circle of
aorta   artery   artery   thoracic   willis
                                         aorta

↓   ↓
mc vessel   least comon
affected   vessel affected

Aneurysm   00:29:44

Bulging / dilatation of a vessel wall.

True
Involves all 3 layers of
    blood vessel.

Pseudo/False
→ Due to extra
   vascular hematoma
   communicates with in
   vessel Lumen
→ mc cause : post MI
   rupture

→   mc cause of aortic aneurysm: atherosclerosis

syphilitic aneurysm :
-   aka leutic aneurysm.
-   occurs in tertiary syphilis. t.me/latestpgnotes
-   usually affects ascending aorta and vasa vasorum.
-   Tree-bark appearence

Syphilitic   Lung
aneurysm   histoplasmosis

myotic aneurysm :

- Caused by Staphylococcus aureus.
- Occurs in femoral artery.

VASCULAR TUMORS

Classification of vascular tumors   00:00:13

Benign	Intermediate	Malignant
• Hemangioma	• Kaposi sarcoma	• Angiosarcoma
• Lymphangioma	• Hemangioendothelioma	• Hemangio-pericytoma
• Glomus tumors		• Lymphangio-sarcoma
• Pyogenic granuloma		
• Bacillary angiomatosis		

Hemangioma   00:02:36

Capillary
- Usually in children
- Skin involvement.
- Self regressing.

H & E :– Proliferation of small blood vessels.

Cavernous
- Seen in children, adults
- Involves internal organs, liver and spleen
- Not self regressing

HPE : Large dilated vascular spaces
→ Can be associated with Von-Hippel Lindau syndrome (gene on chromosome 3)

Active space

Lymphangioma

00:06:32

→ Proliferation of lymphatics
→ 2 Types :
① Capillary lymphangioma
② Cavernous lymphangioma
↓
Cystic Hygroma
↓
Associated with
"Turner's Syndrome"
- No RBCs in lumen
- lymph – pinkish in colour.

Lymphangioma

Pyogenic granuloma :

- A/K/A granuloma gravidarum
- red pedunculated lesion occurs in pregnancy.
- Can regress post pregnancy

Bacillary angiomatosis :

- Associated with Bartonella henselae
infection

Glomus tumor

- Extremely painful tumor.
- affects glomus bodies in pulp of digits.
(Thermoregulation bodies)

Kaposi sarcoma

00:10:54

→ 2nd MC malignancy in HIV patients
→ Organism : HHV – 8 (Human herpes virus)

HHV-8 associated

Kaposi sarcoma | multicentric castleman's disease | Primary effusion lymphoma | Plasmablastic lymphoma.

Active space
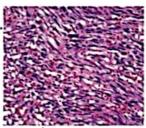
4 Types of Kaposi's sarcoma.

Chronic/ Classic/ European	African/ Endemic	Transplant associated / Immuno- supressed patient	HIV associated ↓ HIV ⊖ve
HIV ⊖ve	HIV ⊖ve	HIV ⊕ve	
Skin is involved	Lymph node involvement	Skin, Lymph Node, Visceral organs	Skin, Lymph Node, Visceral organs
Elderly	<40 yrs	any age	any age

H & E : Spindle cells with RBCs in between.

"Spindle cells"

Kaposi's sarcoma

Angiosarcoma & lymphangiosarcoma   00:17:12

- Can affect skin, liver.
- Hepatic angiosarcoma associated with :
  1) PVC.
  2) Arsenic
  3) Thorotrast

- IHC marker :

  vWF, factor VIII, CD 31, VEGF

Lymphangiosarcoma :

  Usually occurs at sites of :
  1) Chronic lymphedema
  2) Post modified radical mastectomy patients.

Active space
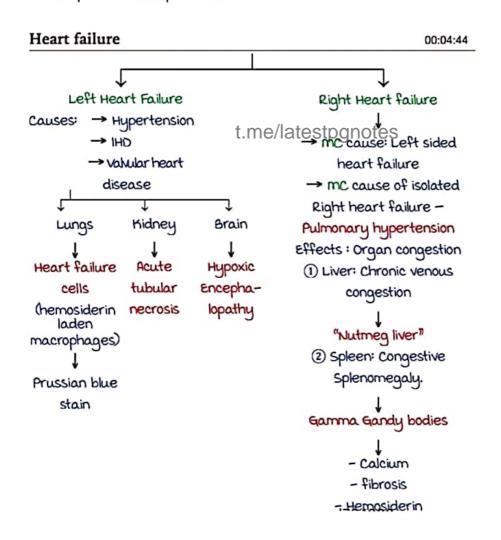
CARDIOVASCULAR SYSTEM

Introduction 00:01:15

→ Heart lined by 3 layers:
① Epi/Pericardium – outermost layer.
② Myocardium – middle – muscular layer.
③ Endocardium – innermost.

Effects of aging on heart:

① Lipofuscin deposition.
② Basophilic degeneration of cardiac myocytes.
③ Lambl's excrescences.
④ ↑ amount of epicardial fat.

Heart failure 00:04:44

Left Heart Failure

Causes: → Hypertension
→ IHD
→ Valvular heart disease

| Lungs | Kidney | Brain |

Lungs ↓
Heart failure cells
(hemosiderin laden macrophages)
↓
Prussian blue stain

Kidney ↓
Acute tubular necrosis

Brain ↓
Hypoxic Encepha-lopathy

Right Heart failure
↓
→ MC cause: Left sided heart failure
→ MC cause of isolated Right heart failure –
Pulmonary hypertension
Effects : Organ congestion
① Liver: Chronic venous congestion
↓
"Nutmeg liver"
② Spleen: Congestive Splenomegaly.
↓
Gamma Gandy bodies
↓
- Calcium
- fibrosis
- Hemosiderin

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Active space

Ischemic heart disease   00:10:14
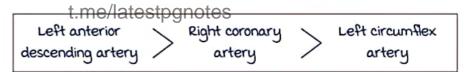
→ 4 categories:
  ① Angina
  ② myocardial Infarction
  ③ Chronic ischemic heart disease.
  ④ Sudden cardiac death

myocardial Infarction: (mI)

→ An area of coagulative necrosis in heart
→ Caused by acute plaque change

2 types

Transmural   Subendocardial

Involves all 3 layers of heart.   Involves only the
  - most common   subendocardial zone
- aka ST segment elevation   - aka Non ST segment
        infarct   elevation infarct

→ mc vessel affected in mI: Left anterior descending artery.

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| Left anterior descending artery | > | Right coronary artery | > | Left circumflex artery |

Warning : Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with marrow Edition 4 videos.

Myocardial response (in conjunction with hypoxia)   00:15:02

Feature	Time
• Onset of ATP depletion	Seconds
• Loss of contractility	< 2 mins
• ATP reduced to 50% of normal	10 mins
• ATP reduced to 10% of normal	40 mins
• microvascular injury	1 hour

Active space
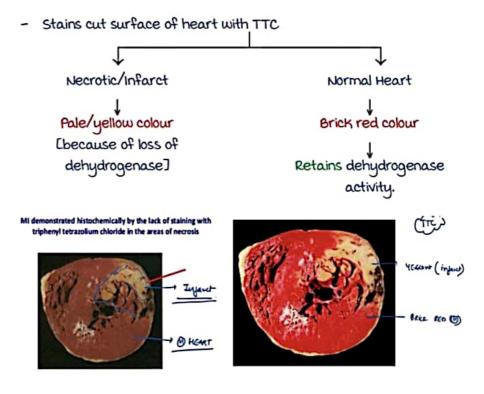
morphologic changes in heart after MI:

→ Within half an hour	→ Injury is reversible.
after half an hour	→ Injury is irreversible.
→ For 4 hours	→ no gross changes
→ In 1ˢᵗ 24 hrs	→ - early neutrophilic infiltrate
	- Contraction band necrosis.
→ In 1-3 days	→ coagulation necrosis and Interstitial infiltrate of neutrophils
→ In 3-7 days	→ - disintegration of dead myofibers, dying neutrophils
	- early phagocytosis - macrophages
→ In 7-10 days	→ granulation tissue at margins.
→ In 10-14 days	→ - well established granulation tissue
	- Collagen deposition
→ > 2 months	→ Dense collagenous scar.

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Histopathology   00:25:00

→ MI within 1-3 days.

mild neutrophilic inf.

MI is aru < 3 days

Brisk neutrophilic infiltrate

→ MI less than 12 hrs can be detected by

↓

TTC Stain - "Triphenyl tetrazolium chloride"

Active space

- Stains cut surface of heart with TTC

Necrotic/Infarct → Pale/yellow colour [because of loss of dehydrogenase]

Normal Heart → Brick red colour → Retains dehydrogenase activity.

MI demonstrated histochemically by the lack of staining with triphenyl tetrazolium chloride in the areas of necrosis

Clinical features, markers and complications of MI   00:29:42

→ Clinically:
ECG changes:
① ST Segment elevation
② T wave inversion.
③ Pathological Q waves.

Biochemical markers after MI:

① LDH — 5 iso enzymes (LDH 1, 2, 3, 4, 5]
→ Normal: LDH2 > LDH 1
In MI: LDH1 > LDH2 → LDH Flip.

② myoglobin
→ earliest to increase after MI
→ non – specific marker.

③ Troponin I and T
→ measured in blood levels.
→ most specific marker → Trop I

④ CK–MB
→ Level raises in MI

Complication: [ACT RAPID – mnemonic]
① Aneurysm
② Contractile dysfunction

Active space

③ Thrombus
④ Ventricular free wall rupture
⑤ Arrythmias
    – Within 1 hr → ventricular fibrillation
    – After 1 hr → supra ventricular tachycardia
⑥ Pericarditis
    ↓

    "Dressler's Syndrome"
    ↓

Post MI fibrosuppurative pericarditis
→ Occurs within 2-3 days of MI
→ Autoimmune reaction

Ischemia reperfusion injury   00:36:35

After stenting or treatment of a patient for MI
↓
Symptoms get worsened
↓
Ischemia reperfusion injury
↓
because of free radicals, complement activation

H ९ E:
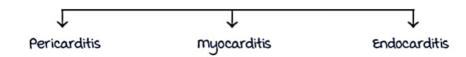
    Contraction band necrosis

Carditis   00:38:51

Pericarditis   Myocarditis   Endocarditis

Pericarditis:

    Acute   Chronic
    ↓   ↓
Exudation of fluid   Can cause fibrosis

① Serous – watery exudates   Chronic
    Eg. SLE, RHD   Constrictive
② Fibrinous exudates – MC   Pericarditis
    Eg. RHD, MI
③ Pus in Infection like bacterial, viral etc.
④ Caseous exudates – TB
⑤ Haemorrhagic exudates – malignancies.

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Active space

Pathology • v2.0 • Marrow 4.0 • 2020

Myocarditis and endocarditis 00:42:10

myocarditis:

- MC helminthic cause: Trichinella spiralis.
- MC virus: Coxsackie A & B, Herpes

Endocarditis:

① Rheumatic fever and Rheumatic heart disease.
- Immunologically mediated multi system disease.
- Type II Hypersensitivity reaction
- Age: 5-15 years
- Usually occurs 2-3 weeks after sore throat with
  β hemolytic streptococci

              ↓
  [Strain: 1, 3, 5, 6, 18]
→ Streptococcal M Protein cross reacts with glycoprotein in heart and joints.

                    ↓
              "molecular mimicry"
→ MC valve affected – mitral valve
→ Least common valve affected – Pulmonary valve.
→ In acute rheumatic fever – mitral regurgitation
→ In chronic rheumatic heart disease – mitral stenosis.

Revised Jones criteria 00:47:16

major Criteria:
① Joints – migratory Polyarthritis – (Non erosive)
② Subcutaneous nodules – (Painless, extensor surface of palms and soles)
③ Erythema marginatum (except face)
④ Sydenham's chorea
⑤ Carditis (Pericarditis)

minor criteria:
- Fever, Poly arthralgia
- ↑ ESR & CRP, prolonged PR interval
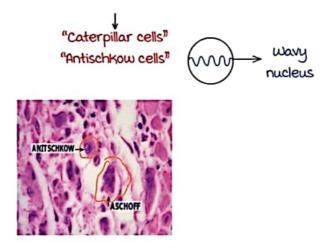
Morphology of heart in RHD 00:50:14
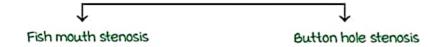
① Aschoff bodies:
- Pathognomonic for RHD
- Consist of lymphocytes, plasma cells, giant cells, fibrinoid necrosis, collagen
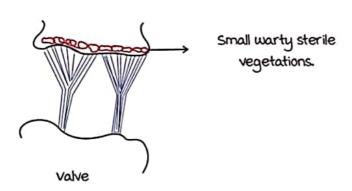
              +
cells with wavy, slender, ribbon like nucleus

Active space

↓
"Caterpillar cells"
"Antischkow cells" 〰 → Wavy nucleus

ANITSCHKOW→
ASCHOFF
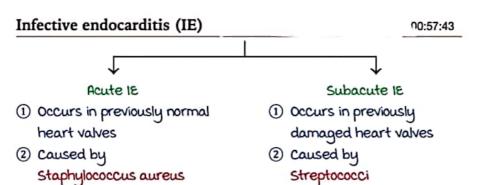
② Bread and butter pericarditis.
③ McCallum plaques/Subendocardial jets
  - Posterior wall of left atrium.
④ In chronic rheumatic heart disease.

Fish mouth stenosis   Button hole stenosis
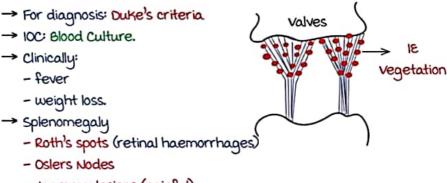
  - because of fibrosis and mitral stenosis.
⑤ Vegetation:
  - small, warty, verrucous vegetation
  - along the lines of closure of valve leaflets.
  - sterile

→ Small warty sterile vegetations.

Valve

Infective endocarditis (IE)   00:57:43

Acute IE   Subacute IE
① Occurs in previously normal   ① Occurs in previously
   heart valves   damaged heart valves
② Caused by   ② Caused by
   Staphylococcus aureus   Streptococci

→ For diagnosis: Duke's criteria
→ IOC: Blood Culture.
→ Clinically:
  - fever
  - weight loss.
→ Splenomegaly
  - Roth's spots (retinal haemorrhages)
  - Oslers Nodes
  - Janeway lesions (painful)
→ MC infected valves: mitral and aortic valve.

valves

IE
vegetation

Vegetations:

Large, bulky, irregular, friable, destructive, infected vegetations
↓
along the lines of closure.

Non-Bacterial Thrombotic Endocarditis – NBTE, Libmann Sachs endocarditis   01:01:48
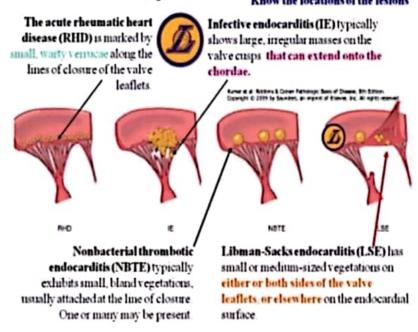
NBTE:
- Patients with debilitating diseases like metastatic carcinoma of pancreas, AML-m3,
- small flat vegetations along the lines of closure seen.

Libman Sachs Endocarditis:
→ Seen in SLE Patients.
→ Small – medium sized, sterile vegetations
→ Seen on both sides of valve leaflets.
  (mc on under surface)
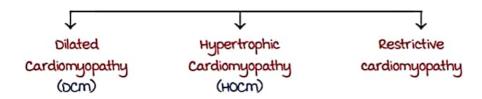
Figure 12-25 Comparison of the four major forms of vegetative endocarditis. Know the locations of the lesions

The acute rheumatic heart disease (RHD) is marked by small, warty verrucae along the lines of closure of the valve leaflets

Infective endocarditis (IE) typically shows large, irregular masses on the valve cusps that can extend onto the chordae.

Robbins & Cotran Pathologic Basis of Disease, 8th Edition
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RHD   IE   NBTE   LSE

Nonbacterial thrombotic endocarditis (NBTE) typically exhibits small, bland vegetations, usually attached at the line of closure. One or many may be present.

Libman-Sacks endocarditis (LSE) has small or medium-sized vegetations on either or both sides of the valve leaflets, or elsewhere on the endocardial surface.

Active space

Cardiomyopathy   01:04:54

Dilated Cardiomyopathy (DCM) → Hypertrophic Cardiomyopathy (HOCM) → Restrictive cardiomyopathy

Dilated cardiomyopathy:

→ Causes:
① Idiopathic (> 50%)
② Alcohol
③ Post partum
④ Myocarditis
⑤ Drugs: Adriamycin
⑥ Haemochromatosis.
⑦ Genetic mutation of "Titin" – largest known protein in human body.

→ Dilatation of all 4 chambers of heart – "Flabby hypocontracting heart"

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HOCM and restrictive cardiomyopathy   01:08:13

HOCM:
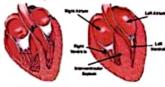
Causes:
① Genetic : β myosin heavy chain.
→ MC cause of sudden cardiac death in young athletes.
→ Selective hypertrophy of interventricular septum
        ↓
   "Banana split configuration"

Banana split configuration

Hypertrophic Cardiomyopathy

HPE:
- myofiber hypertrophy
- "Helter skelter myofiber disarray"

Restrictive cardiomyopathy:
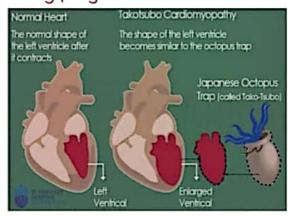
Causes:
① Amyloidosis – MC cause – transthyretin amyloidosis
② Metastatic cancer
③ Sarcoidosis

④ Any granulomatous lesion.
⑤ Loeffler endoradiation
⑥ Scleroderma
⑦ Haemochromatosis — dilated > restricted.

Takotsubo cardiomyopathy:

Normal Heart — The normal shape of the left ventricle after it contracts

Takotsubo Cardiomyopathy — The shape of the left ventricle becomes similar to the octopus trap

Japanese Octopus Trap (called Tako-Tsubo)

Left Ventrical

Enlarged Ventrical

- Sudden emotional distress.
- Shape of left ventricle becomes
  ↓
  Similar to octopus trap

Cardiac tumors   01:13:58

→ mc cardiac tumor – metastasis (Lung ca)
→ mc primary cardiac tumor – Myxoma
→ mc Primary cardiac tumor in children – Rhabdomyoma
→ mc tumor of heart valve – Papillary fibroelastoma
→ mc Primary malignancy of heart – Angiosarcoma
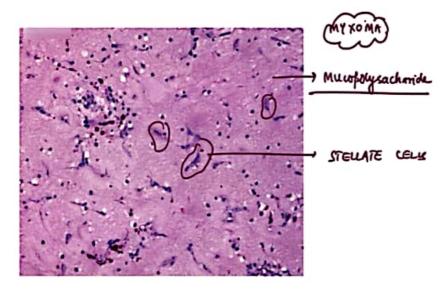
Myxoma:

→ Benign Tumor
-→ Produce: Ball Valve obstruction
→ Usually affects left atrium.
→ Can be associated with Carney syndrome.

Active space

HPE:

- Stellate/Lepidic cells in a mucopolysaccharide background

MYXOMA

→ Mucopolysaccharide

STELLATE CELLS

Rhabdomyoma:

- Can be associated with tuberous sclerosis.
- Usually occurs in ventricles.
- H & E: Spider cells.

Carcinoid heart disease:

- Right side of heart affected.
  Tricuspid reguraitation

Barlow's syndrome:

- Floppy mitral valve / prolapsed mitral valve
- marfans syndrome patients.

  ↓

  MC cause of death – aortic dissection.

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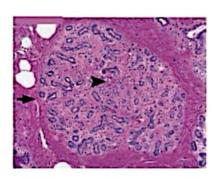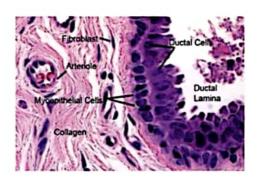
BREAST

Breast   00:00:30

Normal histology
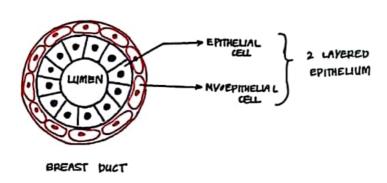
→ Breast ducts   }
→ Breast lobules } Present in stroma

→ Ducts are lined by
 1) myoepithelial layer.
 2) Ductal epithelial cell layer.

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Breast duct

BREAST DUCT

Breast lesions and relative risk of developing invasive CA.

1) Non proliferative breast changes

↓

3% risk of developing invasive ca

2) Proliferative disease without atypia

↓

5-7% risk of developing invasive ca

3) Proliferative disease with atypia

↓

11 - 13% risk of developing invasive ca

4) Carcinoma in situ

↓
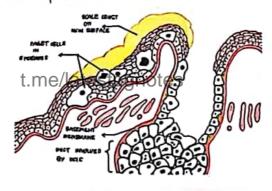
25-30% risk of developing invasive ca

↓

Lobular and ductal carcinoma in situ - highest risk.

Paget's disease of nipple   00:05:09

- can also be present on vulva
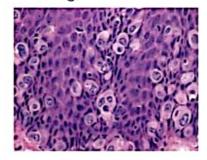
→ Scaly, erythematous eruption of nipple.
→ underlying ductal carcinoma in situ.
→ can progress to malignancy.
→ clinically: pruritis
→ D/D: Eczema (bilateral)
→ usually unilateral.

Histopathology

Paget's cells

→ Large cells, pale, vacuolated cytoplasm with perinuclear clearing.
→ Prominent nucleoli / hyperchromatic nucleus.

Active space

→ Estrogen and Progesterone negative and over express HER2neu.
→ PAS +ve, Diastase resistant.

Carcinoma breast   00:10:20

Risk factors

Familial   Sporadic

Non genetic:
1) Smoking
2) Age
3) Early menarche
4) Late menopause.
5) No breast feeding
6) Nulliparity
7) Age at first Live birth.
8) Family history.
9) Obesity.
10) Estrogen exposure.
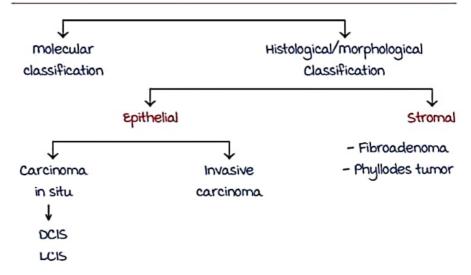
Genetic basis of breast cancer:

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BRCA 1   BRCA 2   P53   CHEK – 2

1) BRCA – 1 gene mutation:
- located on chromosome 17q
- Tumor suppressor gene.
- mutation leads to increase risk of breast, ovarian cancer.
- BRCA 1 positive tumors are triple negative and have medullary like features.
2) BRCA –2 gene mutation:
- located on chromosome 13
- Tumor suppressor gene.
- mutation leads to increase risk of male breast ca, prostate ca
3) P53
- located on chromosome 17
- mc mutated gene in sporadic breast ca
- "Li- Fraumeni Syndrome"
4) CHEK 2 gene
- located on chromosome 22.
- increased risk of breast and thyroid cancer.

Active space
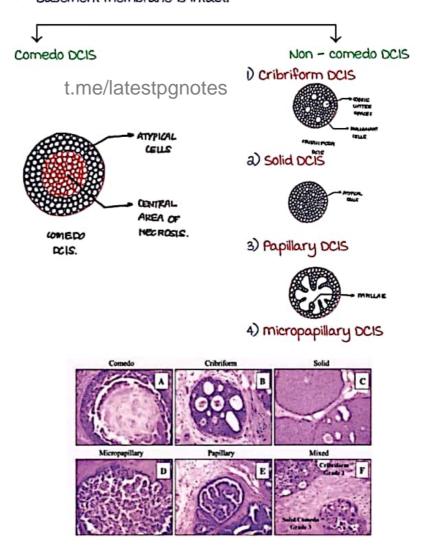
Classification of breast tumors and ductal carcinoma in situ

00:17:38

↓   ↓
molecular   Histological/morphological
classification   Classification

↓   ↓
Epithelial   **Stromal**

↓   ↓   - Fibroadenoma
Carcinoma   Invasive   - Phyllodes tumor
in situ   carcinoma
↓
DCIS
LCIS
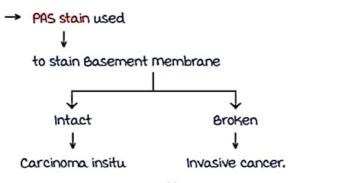
Ductal carcinoma in situ

→ Epithelial proliferation of ductal cells.
→ Basement membrane is intact.

↓   ↓
Comedo DCIS   **Non – comedo DCIS**

1) Cribriform DCIS

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→ ATYPICAL CELLS

→ CENTRAL AREA OF NECROSIS.

COMEDO DCIS.

2) Solid DCIS

→ ATYPICAL CELL

3) Papillary DCIS

→ FRILLAE

4) micropapillary DCIS

| Comedo | Cribriform | Solid |
| Micropapillary | Papillary | Mixed |

→ **PAS stain** used
↓
to stain Basement membrane
```
        ┌──────────┴──────────┐
        ↓                     ↓
     Intact                Broken
        ↓                     ↓
Carcinoma insitu        Invasive cancer.
```
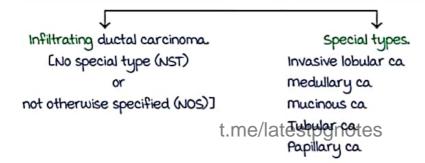
→ **P 63** – marker can differentiate DCIS and Invasive CA.

Lobar carcinoma in situ
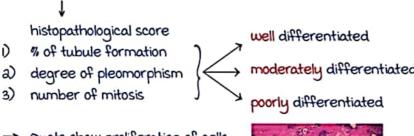
- Incidental finding on biopsy.
- Usually bilateral.

Morphological classification of breast cancer   00:27:07

```
        ┌──────────────────────────┴──────────────────────────┐
        ↓                                                      ↓
Infiltrating ductal carcinoma.                          Special types.
   [No special type (NST)                              Invasive lobular ca
        or                                              medullary ca
not otherwise specified (NOS)]                          mucinous ca
                                                        Tubular ca
                                                        Papillary ca
```

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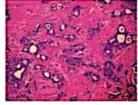
1) **Invasive ductal cancer (NST)**
- presents as hard, irregular mass
- mc morphological type of breast cancer.
- H & E
① Ducts/tubules formation
② Lined by pleomorphic cells (absent myoepithelial layer)
③ mitosis
→ BR – score: **Bloom Richardson score**
↓
histopathological score
1) % of tubule formation   **well differentiated**
a) degree of pleomorphism   }⟷   **moderately differentiated**
3) number of mitosis   **poorly differentiated**

→ Ducts show proliferation of cells
→ Tubule formation
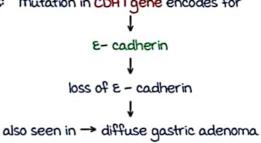
Invasive ductal carcinoma

Active space

Lobular carcinoma and invasive lobular carcinoma   00:32:25

Lobular carcinoma

→ Usually bilateral

→ multicentric

→ Pathogenesis: mutation in CDH I gene encodes for

$$\downarrow$$

ε- cadherin

$$\downarrow$$

loss of ε – cadherin

$$\downarrow$$

also seen in → diffuse gastric adenoma

→ H & ε
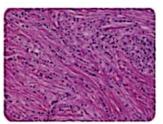
- small, monomorphic dyscohessive cells arranged one after another

$$\downarrow$$
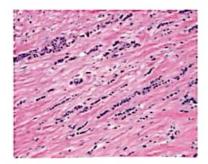
"Indian file"/"Single file"

→ excellent prognosis.

INDIAN FILE/
SINGLE FILE
PATTERN

INVASIVE
LOBULAR
CANCER

→ Signet- ring cells containing an intracytoplasmic mucin droplet are common.

→ Desmoplasia – minimal or absent

Indian file appearence.
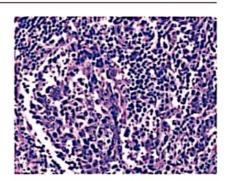
→ Characteristic pattern of spread to Leptomeninges and peritoneum.

$$\downarrow$$

"Carcinomatous meningitis"

Active space

Medullary carcinoma
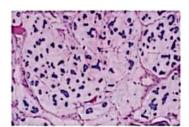
00:38:45
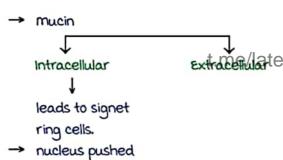
- usually associated with BRCA-1 mutation.
- H & E:
① Sheets (syncytium of highly pleomorphic cells
② mitosis
③ Lymphoplasmacytic infiltrate
④ Pushing borders.
→ BRCA – 1 positive.
   Triple negative.
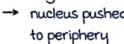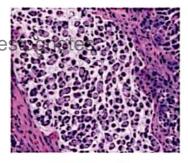
mucinous carcinoma breast:

→ H & E: cells floating in pools or lakes of mucin.
→ Excellent prognosis.

→ mucin

```
          mucin
            |
   ┌────────┴────────┐
   ↓                 ↓
Intracellular    Extracellular
   ↓
leads to signet
ring cells.
```

→ nucleus pushed to periphery

signet ring cells

NUCLEUS
MUCIN ENTERS CELL

NUCLEUS PUSHED TO EDGE
MUCIN FILLS THE CELL.

SIGNET RING CELL
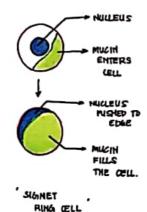
Tubular carcinoma breast:

→ Show large number of tubules.
   ↓
   might have certain shapes (eg: Angulated, Square)
→ Tubules lined by monomorphic cells.

Active space

Molecular classification of breast   00:45:41

→ based on gene expression profiling.
→ based on ER, PR, HER2/neu status.

1) **Luminal A:**
- ER positive, PR positive, HER2/ neu −ve.
- mc type of breast cancer. (60−70%)
- well differentiated, elderly, good prognosis
- Low Ki67 (proliferative index)

2) **Luminal B:**
- ER +ve, PR +ve, HER 2/neu +ve.
- Triple positive
- Well− moderately differentiated
- good prognosis
- Ki67 can be low or high

3) **Basal like:**
- ER −ve, PR −ve, HER 2/neu −ve.
- Triple −ve
- Poorly differentiated, poore prognosis.
- Ki 67−high.
- young, premenopausal women.
- BRCA −1 +ve usually.

4) **HER 2/neu positive tumour:**
- ER −ve, PR −ve,
- Poorly differentiated
- Poor prognosis.
- Ki 67− high

5) **Claudin Low type:**
- triple negative type.
- reduced expression of Claudin − genes , and cell to cell adhesion molecules − 3,4,7   Targetted therapy Tamoxifen.
                                          good prognosis

ER, PR, HER 2 neu receptors   00:53:24
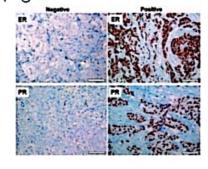
- If tumor is ER, PR +ve   →

Trastuzumab/Herceptin
bad prognosis
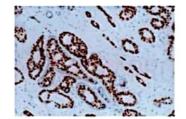
ER − Estrogen receptors
PR − Progesteron receptors
→ If tumor is Her2neu +ve →
                           →
→ ER − PR − nuclear receptors.
→ Her − 2 − neu − membranous
                  receptor

Active space
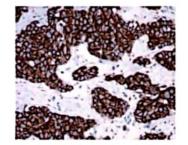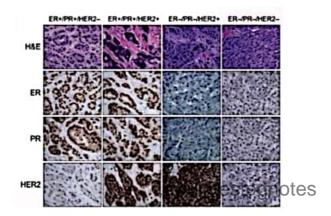
→ PR/ER +ve → Immunohistochemistry

⤷

" Brown colour."

→ Brown stained nuclei

→ HER 2/neu – membranous receptor

→ membrane shows brown colour.

⤷

HER 2/neu +ve.

Allred scoring system: 00:58:31

→ Allred scoring system:

 – for ER and PR

① Proportion score:

0 – No cells +ve

1 – < 1% cells +ve

2 – 1 – 10 % cells +ve

3 – 11 – 33 % cells +ve

4 – 34 – 67% cells +ve

5 – 67 – 100% cells +ve

② Intensity score

0 – Negative

1 – mild

2 – moderate / intermediate.

3 – strong

→ Allred score = proportion score + intensity score.

IHC for HER 2/neu:

0
1 } HER 2/neu negative

2 → Flourescent Insitu Hybradisation - FISH test

3 → Her 2 neu positive

→ after FISH we calculate → $\dfrac{HER\ 2/neu}{CEP\ 17}$ = > 2.2

$\downarrow$

HER 2/neu +ve

Prognostic factors   01:02:43

→ most important prognostic factor in absence of metastasis

$\downarrow$

Axillary Lymph node status.

→ most important prognostic factor in the presence of metastasis.

$\downarrow$

ER, PR, HER 2/neu receptor.

→ TNM staging

→ Stage of tumor

→ Size of tumor

→ Type of tumor
  ± Infiltrating ductal ca - poor prognosis
  Special types - good prognosis.

→ molecular types.

Phyllodes tumor:

→ aka cystosarcoma phyllodes

$\downarrow$

"leaf Like pattern"

→ HPE:
  1) cellularity
  2) mitosis
  3) Stromal overgrowth
  4) Infiltrative borders.
  } differentiate it from fibroadenoma.
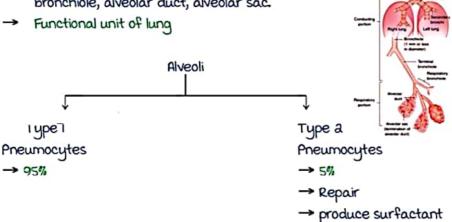
Active space

RESPIRATORY SYSTEM

Anatomy of lung   00:01:08

- Acinus :
- → combination of respiratory bronchiole, alveolar duct, alveolar sac.
- → Functional unit of lung

Alveoli

Type 1 Pneumocytes	Type 2 Pneumocytes
→ 95%	→ 5%
	→ Repair
	→ produce surfactant
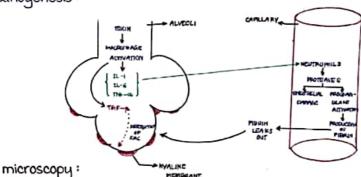
- Histology :
- → Entire respiratory tract is lined by pseudostratified ciliated columnar epithelium. (Except vocal cords → stratified squamous epithelium)

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Adult respiratory distress syndrome   00:03:35

- A/K/A Acute Lung Injury (ALI) / Diffuse Alveolar Damage (DAD) / Hyaline membrane disease
- Pathogenesis :

- microscopy :
- → Hyaline production and deposition in sacs :
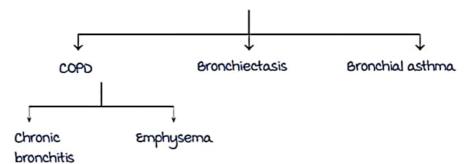
- X-ray : Bilateral diffuse infiltrate → white-out appearance

Active space
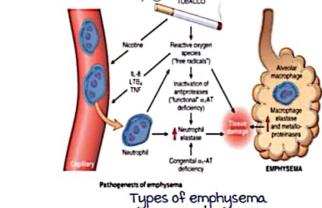
Obstructive lung diseases

00:08:16

```
                        Obstructive lung diseases
                    ┌──────────────┬──────────────┐
                    ↓              ↓              ↓
                  COPD       Bronchiectasis   Bronchial asthma
              ┌─────┴─────┐
              ↓           ↓
           Chronic     Emphysema
           bronchitis
```
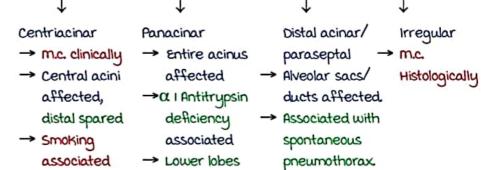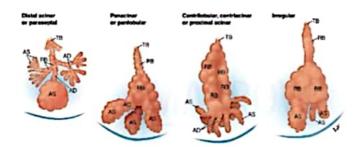
Emphysema
- Irreversible dilatation and destruction of air spaces distal to the terminal bronchioles.
- Involves : - Respiratory bronchioles
            - Alveolar ducts
            - Alveolar sac
- Pathogenesis :
  → Smoking
  → α 1 Antitrypsin deficiency
  normal lung : perfect balance between elastases and anti elastases (α 1 Antitrypsin)
→ Smoker : ↑ elastase and destructions
→ α 1 antitrypsin deficiency : ↑ Elastases

Pathogenesis of emphysema

Types of emphysema

```
        ┌──────────────┬──────────────┬──────────────┐
        ↓              ↓              ↓              ↓
   Centriacinar    Panacinar    Distal acinar/   Irregular
                                paraseptal
```

Centriacinar
→ m.c. clinically
→ Central acini affected, distal spared
→ Smoking associated
→ upper lobes

Panacinar
→ Entire acinus affected
→ α 1 Antitrypsin deficiency associated
→ Lower lobes

Distal acinar/paraseptal
→ Alveolar sacs/ducts affected
→ Associated with spontaneous pneumothorax

Irregular
→ m.c. Histologically

Active space

- Gross : bullae due to destruction of walls
- C/F- pursed lip breathing (pink puffers)

Chronic bronchitis   00:18:05

- Persistent productive cough for at least 3 months, in at least 2 consecutive years in absence of any other identifiable cause
- 90% → smokers
- pathogenesis: →   Smoking
                      ↓
              epithelial irritation
                      ↓
              ↑↑ mucus production

↑ Reid index   ↑ risk of 2° infections
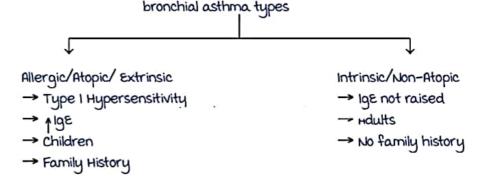
→ Goblet cell hyperplasia
   Reid index
→ ratio of thickness of mucous gland layer to thickness of basement membrane between epithelium and cartilage

→ $= \dfrac{bc}{ad}$

→ Normal = 0.4
→ ↑ in chronic bronchitis.
• premalignant condition

Bronchial Asthma   00:22:27
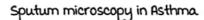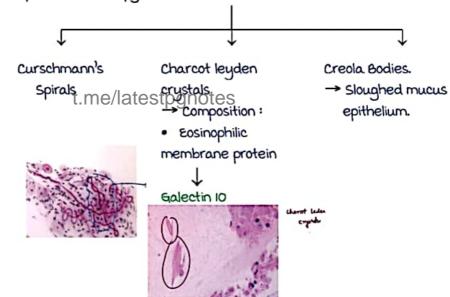
- Reversible bronchoconstriction and inflammation of airways.
- Type I hypersensitivity reaction

bronchial asthma types

Allergic/Atopic/ Extrinsic
→ Type I Hypersensitivity
→ ↑IgE
→ Children
→ Family History

Intrinsic/Non-Atopic
→ IgE not raised
→ Adults
→ No family history

Genetics in asthma

1. IL-13 gene Polymorphism
2. ADAM 33 Polymorphism
3. Gene for atopy → Chromosome 5q
4. ↑↑ YKL 40 → ↑ Severity

Sputum microscopy in Asthma

Curschmann's Spirals

Charcot leyden crystals
→ Composition :
- Eosinophilic membrane protein
↓
Galectin 10

Creola Bodies.
→ Sloughed mucus epithelium.

Charcot leden crystals

- Airway remodelling :
→ ↑ Fibrosis
→ ↑ Vascularity
→ ↑ Smooth muscles

Bronchiectasis   00:31:27
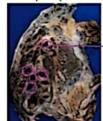
- Abnormal permanent dilation of bronchi and bronchioles
- Causes :
  1. Kartagener's syndrome
→ A/K/A immotile cilia syndrome / 1° ciliary dyskinesia (mutation in dynein arm of cilia)

Active space

→ Triad : Sinusitis
        situs inversus
        bronchiectasis
→ male + Female infertility
2. Cystic fibrosis ⎫
3. Obstruction ⎬ lower lobes
4. Infection   ⎭

• IOC → HRCT
• Gross specimen :
→ In normal lung : probe stops 1-4 cm before the pleura.
→ In bronchiectasis : probe reaches almost upto pleura.
• Complications :
→ Empyema
→ Lung abscess
→ Amyloidosis (AA)

Restrictive lung disorders   00:37:15

```
                    ┌──────────┴──────────┐
                    ↓                      ↓
Fibrosing lung Disorders        t.me/latestpgnotes    Pneumoconiosis
```
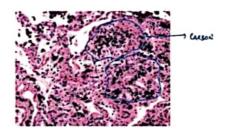
Pneumoconiosis
• A/K/A occupational lung disease
• Important factors for development of pneumoconiosis :
1. Size of particles : <5 microns are dangerous
2. Solubility of particles
3. Duration of exposure
4. Synergetic factors(like smoking)

Coal Worker's pneumoconiosis :
• Usually affects upper lobes
• Pathologically it can be of 3 types:
→ Asymptomatic anthracosis
→ simple coal worker's pneumoconiosis → coal macules
                                      ↳ coal nodules
→ complicated coal worker's pneumoconiosis → Progressive
                                             massive Fibrosis

→ Carbon
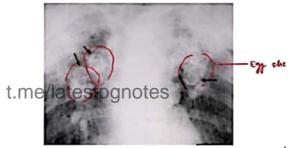
- Caplan syndrome
→ combination of coal worker's pneumoconiosis +
  Rheumatoid Arthritis

Silicosis and Asbestosis   00:43:05

Silicosis

- A/K/A miner's/ Grinder's Disease
- m.c occupational lung disease in the world
- m.c particle causing silicosis → Quartz (SiO_2)
- ↑ Risk of → TB & Cancer

- X - ray: Egg shell calcification (lymph nodes)

→ Egg she

- Produces Nodular Fibrosis of Lung.

Asbestosis
- shipping industry
- 2 types:

Serpentine	Amphibole
-Affects lower lobes	- more pathogenic
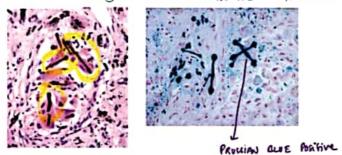
- Diseases caused by Asbestos:
→ Pleural plaque (m.c lesion)
→ Pleural nodules
→ Lung cancer (m.c malignancy)
→ malignant mesothelioma (most specific)

Active space

- H & E: Asbestos / Ferruginous Bodies (dumbbell shaped Bodies)

PRUSSIAN BLUE Positive
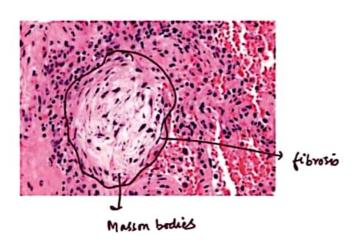
Different pneumoconiosis:

Bagassosis → sugarcane toxicity
Byssinosis → Cotton toxicity
Siderosis → Iron toxicity
Stannosis → Tin toxicity
Berylliosis → Beryllium → Nuclear industry
         ↳ Non caseating granulomas

Warning : Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with marrow Edition 4 videos.

Fibrosing restrictive lung disorders   00:50:15

1. Usual interstitial pneumonia (UIP)/ Idiopathic pulmonary fibrosis
   → usually caused by TGF - β   t.me/latestpgnotes
   → Honeycomb lung
2. Non-Specific interstitial pneumonia
   → No Fibrosis
   → No honeycombing
3.   Cryptogenic organising pneumonia
→   BOOP (bronchiolitis obliterans organising pneumonia)
→   HPE : masson bodies

fibrosis

Masson bodies

Active space
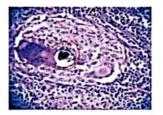
INFECTIONS AND GRANULOMAS OF LUNG

Granulomatous disorders of lung - sarcoidosis   00:00:12

- Females >> males
- Type IV hypersensitivity
- CD4THI - granuloma.
- Immunologically medicated -   HLA - AI }
                                 HLA- B8 } m.c associations
- C/F - Eye - uveitis
- Salivary gland - Sicca Syndrome
- Lung - m.c affected
- Hilar lymph node enlaraement
- Skin, genitals, bone marrow can be affected

Sarcoidosis - histopathological examination   00:02:38

on Histopathological examination (H§E)

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Non caseating/ Naked granulomas	Asteroid bodies	Schaumann bodies
• epitheloid cells, collar of lymphocytes around them and gait cells	• Star shaped Inclusions in giant cells	• Basophilic Ca^{2+} Concretions.

• Naked granuloma -
↓
Absence of lymphocyte collar

Lymph node biopsy – Non caseating granuloma.

Active space

Asteroid body

Schaumann body

Other investigation findings
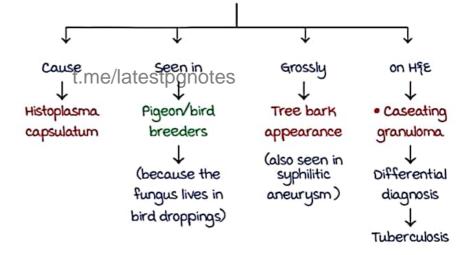
- ↑ Angiotensin converting enzyme levels

- ↑ Ca^{2+} → causes metastatic calcification

- ↑ CD4 : CD8 ratio (Normal is 2:1)

- Kveim's test positive
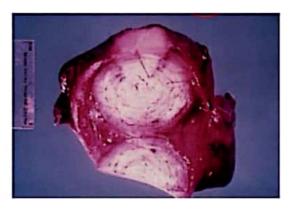
Hypersensitivity pneumonitis and histoplasmosis   00:08:33

- It is an example of – both Type III and Type IV hypersensitivity

- Honey combing and fibrosis in the lung

Histoplasmosis

Cause	Seen in	Grossly	on H&E
Histoplasma capsulatum	Pigeon/bird breeders	Tree bark appearance	• Caseating granuloma
	(because the fungus lives in bird droppings)	(also seen in syphilitic aneurysm)	Differential diagnosis
			Tuberculosis

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Lung in histoplasmosis

Active space

Tuberculosis   00:12:24

- Caused by mycobacterium tuberculosis

$$\downarrow$$

Acid – fast – bacilli (AFB)

$$\downarrow$$

Staining by- Zeihl- nelson stain
(Z-N stain)

AFB positive organisms

my- mycobacterium tuberculosis

Nose- Nocardia

Is – Isospora

Cold – Cryptosporidium

and

Hot – Hooklets of hydatid cyst
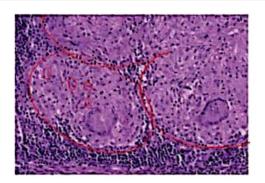
AFB
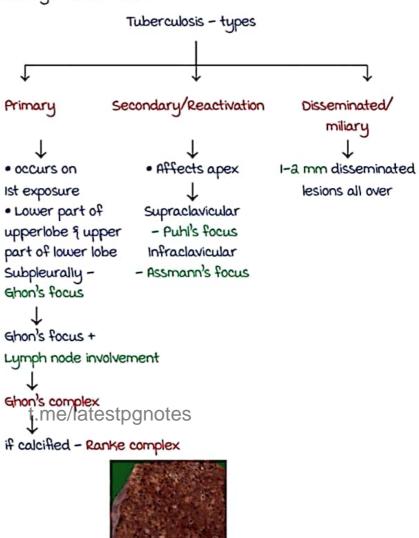
- AFB – Commonly seen in necrotic area

  Acid fast bacilli – due to presence of mycolic acid

  Virulence – cord factor.

Tuberculosis - histopathological examination   00:16:07

Active space
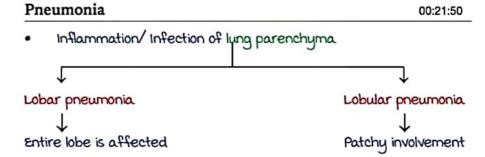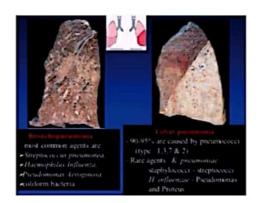
Epitheloid cells surrounded by lymphocyte collar

Langhan's giant cells (horse shoe/ slipper shaped arrangement of nuclei)

Tuberculosis – types

Primary	Secondary/Reactivation	Disseminated/miliary
• occurs on 1st exposure • Lower part of upperlobe & upper part of lower lobe Subpleurally – Ghon's focus	• Affects apex ↓ Supraclavicular – Puhl's focus Infraclavicular – Assmann's focus	1-2 mm disseminated lesions all over

Ghon's focus +

Lymph node involvement

↓

Ghon's complex

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↓

if calcified – Ranke complex

miliary – TB

Pneumonia   00:21:50

• Inflammation/ Infection of lung parenchyma

Lobar pneumonia	Lobular pneumonia
Entire lobe is affected	Patchy involvement

Bronchopneumonia
most common agents are
▸ Streptococcus pneumoniae
▸ Haemophilus Influenza
▸ Pseudomonas Aeruginosa
▸ coliform bacteria

Lobar pneumonia
- 90-95% are caused by pneumococci
  (type 1,3,7 & 2)
- Rare agents K. pneumoniae
  staphylococci - streptococci
  H. influenzae - Pseudomonas
  and Proteus

- **M.C.C of community acquired pneumonia**

  ↓

  Streptococcus pneumonia

  4 stages of lobar pneumonia

Congestion	**Red hepatization**	**Grey hepatization**	**Resolution**
↓	↓	↓	↓
• 1-2 days	• 2-4 days	• 4-8 days	9-10 days
•lung is full of RBCs exudate fluid	• Lung has – liver like consistency	• Grey- due to disintegration of RBCs	**M.C outcome**
	↓		
	Because of fibrin		
	• Red- due to RBCs		

  classification of Pneumonia

Typical	**Atypical**
↓	↓
• cause – bacteria	cause – Viruses, Mycoplasma., Respiratory syncytial virus, Chlamydia pneumonia
	Less exudate
• Lots of exudate	
• Purulent cough	Non purulent cough

Active space
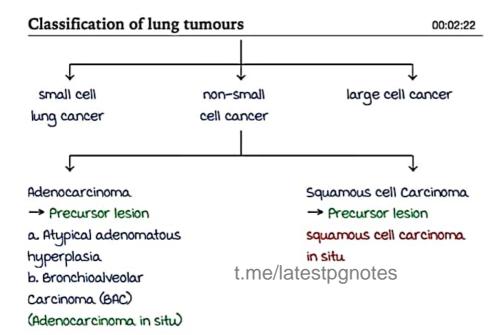
LUNG TUMORS
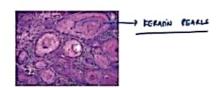
- m.c malignancy of lung: metastasis
- m.c malignancy going to lung: Breast

m.c benign lung tumour : pulmonary hamartoma
   a. Abnormal proliferation of cells
   b. X-Ray: coin shaped lesion

Classification of lung tumours   00:02:22

```
                        |
        +---------------+---------------+
        ↓               ↓               ↓
    small cell      non-small       large cell cancer
    lung cancer     cell cancer
        |               |
        +---------------+
        ↓               ↓
```

Adenocarcinoma   Squamous cell Carcinoma
→ Precursor lesion   → Precursor lesion
a. Atypical adenomatous   squamous cell carcinoma
hyperplasia   in situ
b. Bronchioalveolar
Carcinoma (BAC)
(Adenocarcinoma in situ)

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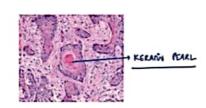
Squamous cell carcinoma of lung   00:04:43

1. Smoking associated
2. m>F
3. Centrally located
4. produce cavitatory lesions
5. Paraneoplastic syndrome (PNS): hypercalcemia due to PTH>PTHrp
            (Parathyroid Hormone related peptide)
6. pathogenesis : p53 gene mutations
- H & E : 1. Keratin pearls
       a. Desmosomes (Adhere 2 squamous cells)

→ KERATIN PEARLS

→ KERATIN PEARL

Active space

- Immunohistochemical marker: CK+ (cytokeratin)
  (IHC)   p63
                                p40

Adenocarcinoma   00:09:48

- M.C lung cancer in women
- Non-smoker
- Peripherally located
- Paraneoplastic Syndrome (PNS) : migratory thrombophlebitis
- Pathogenesis: K-RAS
                  EGFR-I
                  ALF gene
- H & E: glands lined by malignant cells

Adeno Car cinoma
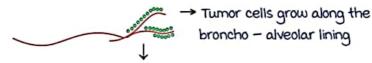
- IHC marker: TTF-I, NAPSIN - A

Bronchioalveolar carcinoma and small cell
carcinoma of lung   00:13:32
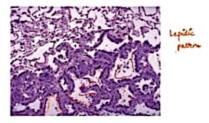
Bronchioalveolar Carcinoma

- Adenocarcinoma in situ
- Good prognosis

→ Tumor cells grow along the
  broncho - alveolar lining
↓

Butterflies on a fence/lepidic/filigree pattern.

Lepidic
pattern

Small cell carcinoma of lung

- Strongest association with smoking
- m>F
- PNS: Cushing syndrome, SIADH (M.C PNS)
- Produces maximum PNS
- Centrally located later→ periphery

Active space
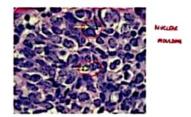
- worst prognosis (most to brain)
- chemosensitive
- Pathogenesis: L-MYC mutation
  - H & E: 1. Small cells
  - 2. Nuclear moulding
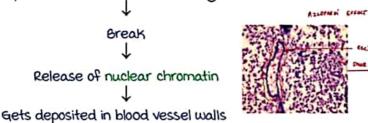
3. Azzopardi effect: Tumour cells (fragile)

$$\downarrow$$

Break

$$\downarrow$$

Release of nuclear chromatin

$$\downarrow$$

Gets deposited in blood vessel walls
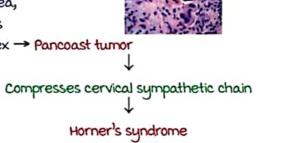
4. Salt and pepper chromatin

- IHC markers: NSE (Neuron Specific enolase)
                Chromogranin
                Synaptophysin
- Electron microscopy: Dense core neurosecretory granules.
- The H & E, IHC markers and electron microscopy findings are same for :
  - → Pheochromocytoma
  - → Carcinoid tumour
  - → Small cell carcinoma of lung
  - → Paraganglioma
  - → Carotid body tumors

Large cell cancer of lung   00:24:47

- Large, pleomorphic cells
- Aggressive tumour
- Paraneoplastic Syndrome: Gynaecomastia
- Clinically: Cough, dyspnea, weight loss, hemoptysis
- Lung cancer at the apex → Pancoast tumor

$$\downarrow$$

Compresses cervical sympathetic chain

$$\downarrow$$

Horner's syndrome

Active space
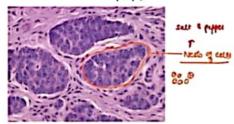
- Components:
  P → Ptosis
  m → miosis
  ε → Enophthalmos
  A → Anhidrosis
  L → Loss of ciliospinal reflex

- Spread

```
              Spread
                │
    ┌───────────┼───────────┐
    ↓           ↓           ↓
 Directly   metastasis  To lymph nodes
    ↓           ↓           ↓
 Recurrent    Brain     Hilar Lymph
Laryngeal nerve           Nodes
    ↓
 Hoarsensess
```
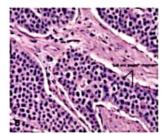
	Squamous cell cancer	Adenocarcinoma	Small cell cancer	Large cell cancer
	m>F Central Smokers	F>m Peripheral non-smokers	m>F Central Smokers	m>F Peripheral smokers – non-smokers
PNS :	Hypercalcemia	migratory thrombophlebitis	Cushing's syndrome, SIADH	Gynecomastia
Pathogenesis :	p53	K-RAS, EGFR, ALK	L-myc	–
H & E :	Keratin pearls	Glands, pleomorphic cells	Nuclear moulding	Large Highly pleomorphic cells.
			Azzopadi effect	
			Salt and pepper chromatin	
IHC :	CK+, p63, p40	TTF-I, NAPSIN – A	NSE Chromogranin synaptophysin +	–

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Carcinoid tumour of lung   00:34:30

- Arise from: Kulchitsky cells
- Clinical presentation:
  → Flushing
  → Sweating
  → Diarrhoea
- H & E: Salt and pepper chromatin.

- Types

Typical	Atypical
1. <2 mitosis/10 HPF	1. 2-10 mitosis/10 HPF
2. No necrosis	2. Necrosis ⊕

Pleural Tumours

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- M.C pleural malignancy : metastasis (Lung mets)

Malignant mesothelioma

- Most specific lung cancer associated with Asbestos exposure
- Duration of exposure : > 25 years
- p53, SV-40 virus
- H & E: Spindle cells
    epitheloid cells
    Sarcomatoid cells
- IHC markers: Calretinin + (Best marker)
        CK 5/6
        WT-1
- Electron microscopy: Long slender microvilli/ tonofilaments

→ Lung adenocarcinoma: short, plump microvilli

Active space
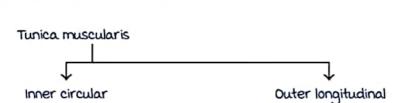
OESOPHAGUS
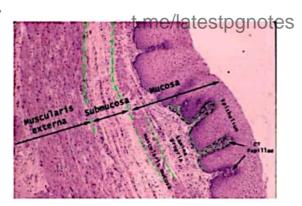
Layers of GIT 00:00:12

- HPE:
    4 Layers:
    - mucosa
    - Submucosa
    - Tunica muscularis
    - Serosa/Adventitia
- Oesophagus does not have serosa

- Gall bladder does not have a submucosa.

Tunica muscularis

Inner circular   Outer longitudinal

Oesophagus

- Oesophagus lined by stratified squamous epithelium.

Barrett's oesophagus 00:03:06

- metaplasia
- Stratified squamous Epithelium

GERD →

Columnar epithelium
↓
Columnar lined ooesophagus (CLO)

Active sp:

Barrett's oesophagus also known as:
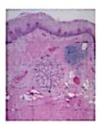
columnar lined oesophagus

Short segment   long segment
< 3 cms   > 3 cms

- Risk factor for adenocarcinoma oesophagus.
- Gross: Red velvety granular mucosa.
- H P E:
  1) Intestinal metaplasia
  2) Goblet cells

This is normal esophageal squamous
mucosa at the top, with underlying
submucosa and muscularis propria
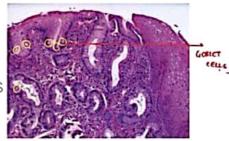
Barrett's esophagus in which there is
gastric-type mucosa above the
gastroesophageal junction. Note the
columnar epithelium to the left and the
squamous epithelium at the right.

- Goblet cells contain mucin
- Goblet cells stained by
  Alcian blue
  ↓
  Stain for mucin

GOBLET CELLS

Tumors of oesophagus   00:09:49

- mc benign esophageal tumor: Leiomyoma.

Oesophageal malignancy

Squamous cell   Adenocarcinoma
carcinoma

- mc esophageal carcinoma in   - mc esophageal CA in western
  India/world wide   world
- Affects middle 1/3rd of   - Affects lower 1/3rd of
  oesophagus   oesophagus
- Risk factors: Smoking, alcohol, - Risk factors: Barrett's
  HPV, nitrosamines, achalasia,   oesophagus.
  esophageal webs, plummer
  vinson syndrome, tylosis
  palmaris.

Histopathology of oesophageal malignancy   00:12:46

HPE of squamous cell carcinoma:

    1)   Keratin pearls ⟵

    2)   Desmosomes
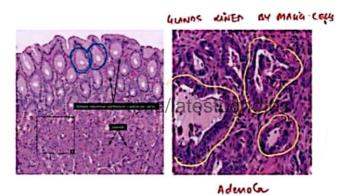
• Immuno histo-chemical marker
    used-Cytokeratin (CK)

Warning : Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with marrow Edition 4 videos.

Adenocarcinoma:

• Glands are lined by malignant cells.

GLANDS LINED BY MALIG-CELL

AdenoCa

• most important prognostic factor for esophageal CA

↓

"Depth of invasion"

Active space

INFLAMMATORY BOWEL DISEASE

IBD	
Crohn's disease	**Ulcerative colitis**
1) Any area of GIT	1) colon & rectum
2) Transmural (all the layes)	2) Submucosal
3) Epidemiology	
– Bimodal ⌈15–20 yrs ⌊Elderly	
– F > m	
– Caucasians	

Pathogenesis of IBD   00:03:04

1. Hygiene hypothesis

   Because of use of lot of preservatives & packed food, lack of
   development of mucosal – immune response.

2. Genetics

   – NOD2 gene polymorphism   t.me/latestpgnotes

   $\downarrow$

   NFK – β pathway

   $\downarrow$

   ↑ Cellular population

   $\downarrow$

   Crohn's disease

   – ATG 16L1 (Autophagy related 16 like)

   – IRGM (Immunity related GTPase-m)

   – IL–23 receptor polymorphism is protective for both Crohn's

disease & Ulcerative colitis

   – HLA association

Crohn's disease	HLA DR 1
Ulcerative colitis	HLA DR 2

Comparison between Crohn's disease &
Ulcerative colitis   00:06:26

Crohn's disease	Ulcerative colitis
m/c site: Ileum, caecum Ileocaecal valve	m/c site: Rectum → colon (Backwash ileitis)

Active space
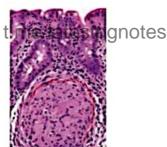
Gross pathology

a) skip lesions

b) Deep Knife like and serpentine ulcer

c) Rubbery thick intestinal wall

d) cobblestone appearance

e) Creeping fat

HPE

1. Transmural involvement

2. CD4THI – non caseating granuloma

3. Cryptitis

4. Crypt abscess

Gross pathology

a) Continuous involvement

b) Superficial broad based ulcer

c) Pseudopolyps (islands of regenerating mucosa)

d) mucosal bridges

e) Toxic megacolon

HPE

1. Submucosal involvement

2. Cryptitis

3. Crypt abscess

Clinical features of Crohn's disease   00:14:49
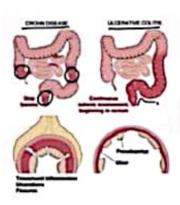
- Intermittent attacks of diarrhea

- Abdominal pain

- Fever

Extra intestinal manifestations

1. Uveitis

2. Primary sclerosing cholangitis

3. Ankylosing spondylitis

4. migratory polyarthritis

Active space

Indeterminate colitis   00:21:10

- 8 – 10% cases where type of IBD can't be made out
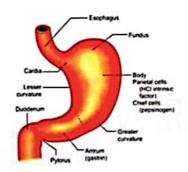
CAN (Colitis Associated Neoplasia) more risk with ulcerative colitis

Crohn's disease	Ulcerative colitis

1. mc site   Ileum
         Cecum
	1. mc site Colon
	         Rectum

2. HLA DR1	2. HLA DR2
3. Smoking – risk factor	3. Smoking – protective
4. Extra intestinal: uveitis, ankylosing spondylitis	4. Primary sclerosing cholangitis
5. CD4 TH1	5. CD4 TH2
6. Skip lesions +	6. –
7. Cobblestone app. +	7. –
8. Deep knife ulcer	8. Superficial broad based ulcer

9. Pseudopolyps   –
    mucosal bridges   –
	9. Pseudopolyp and mucosal
	    bridges are +

10. Transmural	10. Submucosal
11. Wall thick rubbery	11. Toxic megacolon
12. Risk of stricture, fissure fistula & sinus ↑	12. ↓

13. HPE
     Granuloma   +
     Cryptitis & abscess +
	13.
	
	         –
	         + + +

14. Risk of colon Ca ↑	14. ↓
15. Antibody – anti saccharomuces cerevisiae	15. P-ANCA

16. Barium enema
     string sign of Kantor
	16.
	    Lead pipe / Hose appearance

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Active space

STOMACH

- Cells:
  - Parietal cells → HCl, Intrinsic factor
  - chief cells → pepsinogen
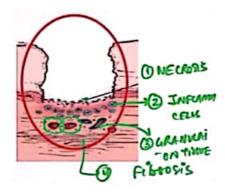
Peptic ulcer diseases   00:01:40

- Defensive forces which protect stomach from injurious stimuli:
  → Surface mucus secretion
  → Bicarbonate secretion into mucus
  → mucosal blood flow
  → Apical surface membrane transport
  → Epithelial regenerative capacity
  → Elaboration of prostaglandins

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- Injurious stimuli
  → H. pylori infection
  → NSAID
  → Aspirin
  → Cigarettes
  → Alcohol
  → Gastric hyperacidity
  → Duodenal gastric reflex

- Ulcer develops when
  Defensive forces ↓, injurious stimuli ↑

- Zones of ulcer
  1. Necrosis
  2. Inflammatory cells
  3. Granulation tissues
  4. Fibrosis

Active space

Peptic ulcer disease

- Can occur in:

Stomach	duodenum
→ Less common	→ More common
→ Location: Lesser curvature near the Incisura angularis	→ Location: D I zone
→ Poorer prognosis	→ Better prognosis
→ Perforation	→ Bleeding (↑ common)
→ No night pain	→ Night pain relieved by food intake
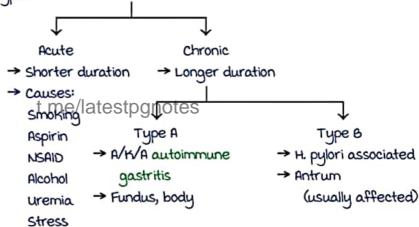
Gastritis   00:07:29

- Inflammation of gastric mucosa.
- Types :

Acute
→ Shorter duration
→ Causes:
  Smoking
  Aspirin
  NSAID
  Alcohol
  Uremia
  Stress

Chronic
→ Longer duration

Type A
→ A/K/A autoimmune gastritis
→ Fundus, body

Type B
→ H. pylori associated
→ Antrum (usually affected)
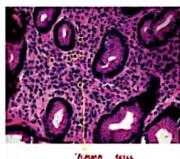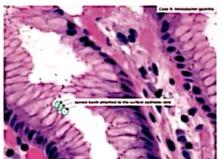
Type B Chronic Gastritis   00:09:22

- m.c
- H. Pylori associated
→ Gram negative bacteria with a tuft of flagella at one end.
→ Only host – humans
→ Virulence factors
  - Flagella → movement of H.pylori in stomach
  - Urease
  - cag A and Vac A toxins → carcinogenic
→ Disease caused by H.pylori
  - chronic gastritis
  - Gastric adenocarcinoma
  - MALTOMA (mucosal associated lymphoid tissues)
→ Usually affects Antrum

Active space

- H&E :
→ Intraepithelial neutrophils and sub epithelial plasma cells
→ H. pylori is found in mucosa (it cannot penetrate the wall)

→ Special stains ──────→ warthin starry silver stain.

→ Non silver stains.
  • Giemsa stain
  • Acridine Orange

Type A chronic gastritis   00:17:12

- A/K/A Autoimmune gastritis
- Spares antrum
- Affects fundus body
- Pathogenesis: Antibodies against parietal cells and against intrinsic factor (IF)

↓

↓ Production of HCl, Intrinsic factor

↓

↑ Gastrin release

↓

Hypergastrinemia

↓ intrinsic factor → deficiency of vitamin B12 absorption → megaloblastic anemia
• Chief cell destruction → ↓ serum pepsinogen concentration.
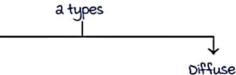
- Clinical Presentation: Pernicious anemia
  ↑ risk of other autoimmune disease
- morphology
  Gross pathology : loss of rugal folds of stomach.
- H & E: infiltrate of lymphocytes and plasma cells

Gastric adenocarcinoma   00:21:50
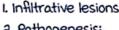
- Risk factors
  1. Smoking
  2. H. pylori → antral
  3. Japanese people
  4. ↑ intake of smoked fish
  5. Food rich in preservatives
  6. Blood Group A
- Site: Antrum > Lesser curvature > Greater Curvature
- Lauren's Classification

a types
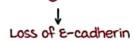
Intestinal	Diffuse
1. Bulky polypoidal lesions	1. Infiltrative lesions
2. Pathogenesis:	2. Pathogenesis:
→ mutation in WNT pathway	→ CDH-1 gene mutation
→ P53 mutation	↓
→ Loss of function in APC	Loss of E-cadherin
3. H & E	
→ Glands lined by malignant cell	3. H & E
4. Better prognosis	→ mucin secretion + Signet Ring cell.
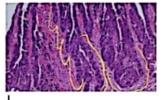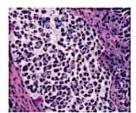
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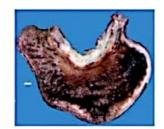
↳ Glands lined by malignant cells

- Linitis plastica
  → Leather bottle appearance
  → Diffusely infiltrates the entire gastric wall without forming an intraluminal mass.

Active space

→ Wall of stomach is thickened up to 2-3 cm
→ Leathery and elastic consistency
→ Develops due to desmoplasia
    (extreme fibrosis in a tumour)

Gastric Adenocarcinoma:
• Clinically: dyspepsia, gastritis
• When if affects

→ Left supraclavicular lymph node → Virchow's node
→ Left axillary lymph node → Irish node
→ Peri umbilical Nodule → Sister mary joseph's
                            nodule

→ Pouch of Douglas → Blumer shelf
→ Ovaries → Krukenberg's tumor

• most important prognostic factor → depth of invasion

Gastro intestinal stromal tumor (GIST)   00:33:20

• m.c mesenchymal tumor of stomach.
• Arises from interstitial cells of cajal.
• Pathogenesis.
    → C-Kit mutation
    → PDGF R-A mutation
• Carney's triad:
    → Gastric GIST
    → Pulmonary chondroma
    → Paraganglioma
• Gross pathology : well circumscribed fleshy mass
• HPE
    → Spindle cells (m.c)   ⬯•   (m.c)
    → Epitheloid cells   ⊙
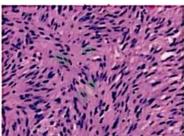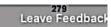
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- Immuno histochemical marker (IHC) :   CD –117 (C–KIT) → most sensitive
  DOG 1 → most specific
  CD–34

- Prognostic Criteria
  → Tumour size :   < 5 cm → Good prognosis
  > 10 cm → bad prognosis
  → Location :   Gastric GIST → Good prognosis
  Intestinal GIST → bad prognosis
  → mitosis: > 10/HPF – bad prognosis

Maltoma and carcinoid tumour   00:38:63

maltoma
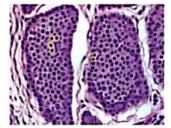
- Usually H.Pylori associated
- MC site of MALT → peyer's patches/ ileum
- MC site of MALToma → stomach
- t (11:18), t (14:18)
- Usually DLBCL (Diffuse Large B Cell Lymphoma)
- HPE : Lymphoepithelial lesions (Lymphocyte entering into a gland)

Carcinoid Tumour

- Arises from enterochromaffin cells.
- Gross pathology : tan brown/yellow colour
- HPE: salt and pepper chromatin
- IHC marker : Neuron specific enolase (NSE)
  Chromogranin
  Synaptophysin
- Electron microscopy : Dense core neurosecretory granules.

salt & pepper chromatin

Active space

MALABSORPTION SYNDROMES AND ULCERS

malabsorption syndromes:

Clinically: Steatorrhea → frothy, bulky greasy stools

| Celiac disease | Whipple's disease | Tropical sprue |

Celiac disease   00:01:25

- Also Known as gluten sensitive enteropathy
- Cannot have:
  - B → Barley
  - R → Rye
  - O → Oats
  - W → Wheat
- Can have rice, maize

Pathogenesis:

Antibody mediated
- → Anti gliadin
- → Anti tissue transglutaminase IgA (most sensitive)
- → Anti endomysial antibody IgA (most specific)

- Gluten contains α − gliadin − cannot be broken by digestive enzyme.
- ↑ CD8+T lymphocyte.
- Associated with HLA − DQ2, DQ8

Clinical features:

- Steatorrhea
- Diarrhea
- Abdominal pain
- Dermatitis herpetiformis (↑ risk)
- Enteropathy associated T cell lymphomas (↑ risk)

microscopy: Villous atrophy
Crypt hyperplasia
↑ Intra epithelial lymphocytes

Active space

- Usually affects the second part of duodenum.

- marsh score

Whipple's disease   00:09:53
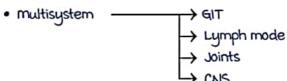
- Caused by – Actinomycete
    ↓
    Tropheryma whipplei
    gram positive organism
- Rare
- multisystem ──────┬──→ GIT
                    ├──→ Lymph node
                    ├──→ Joints
                    └──→ CNS
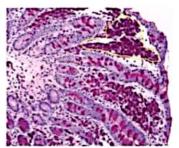
microscopy:

- Lamina propria is studded with foamy macrophages, PAS⁺ diastase resistant organisms
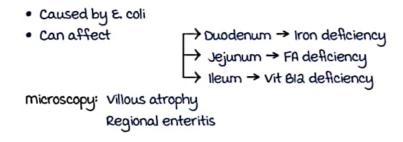
- Differential diagnosis of foamy macrophages on intestinal biopsy:
- Tuberculosis → AFB positive
- Whipple's disease → AFB negative

Active space
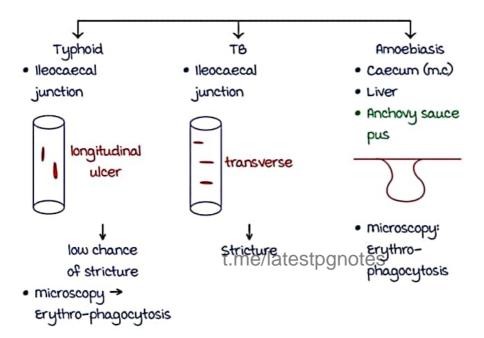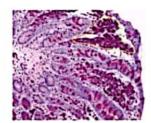
Tropical sprue and ulcers

00:13:26

- Caused by E. coli
- Can affect
  - → Duodenum → Iron deficiency
  - → Jejunum → FA deficiency
  - → Ileum → Vit B12 deficiency

microscopy: Villous atrophy
Regional enteritis

Ulcer of intestine:

Typhoid	TB	Amoebiasis
• Ileocaecal junction	• Ileocaecal junction	• Caecum (m.c)
		• Liver
		• Anchovy sauce pus

Typhoid
longitudinal ulcer
↓
low chance of stricture
• microscopy → Erythro-phagocytosis

TB
transverse
↓
Stricture

Amoebiasis
• microscopy:
Erythro-phagocytosis

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Typhoid fever   Tuberculosis

Active space

POLYPS AND COLON CANCER

Polyps of intestine   00:00:26

- Polyp → Protrusion of mucosa
- Classification of polyp

a.

Polyp
- Sessile (no stalk) → more malignant
- Pedunculated (has stalk) → Less malignant

b.
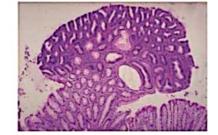
Polyp
- Neoplastic
  - Adenoma
- Non neoplastic
  - Inflammatory
  - Hyperplastic
  - Hamartomatous

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Warning : Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with marrow Edition 4 videos.
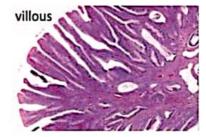
- microscopic classification of Adenoma

  - **Tubular polyp**
    - Has tubules
    - Also Known as adenomatous polyp

  - **Villous polyp**

    Has villous projections

villous

Active space

- Tubulovillous polyp
  - Has both tubules and villous architecture
  - Has highest malignant potential
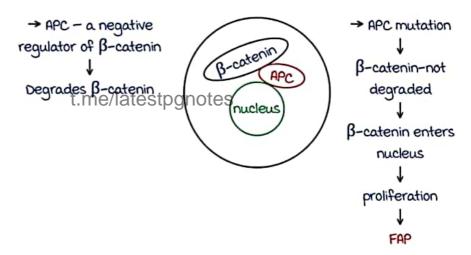
Syndromes related to polyp   00:05:00

1. Peutz-Jeghers Syndrome
   - most common location → Jejunum
   - multiple hamartomatous polyp

            +

   Perioral / mucocutaneous hyper pigmentation
   - Loss of function mutation in LKBI/STKII gene
   - ↑ risk of Carcinoma colon, Breast, Thyroid, Lung etc
2. Familial Adenomatous Polyp (FAP)
   - AD (Autosomal dominant) inheritance
   - APC gene mutation on Chromosome 5q21
     (Adenomatous Polyposis Coli)
- Pathogenesis

→ APC – a negative
regulator of β-catenin
        ↓
Degrades β-catenin

→ APC mutation
        ↓
β-catenin-not
degraded
        ↓
β-catenin enters
nucleus
        ↓
proliferation
        ↓
FAP
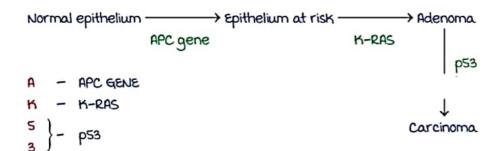
- > 100 polyps are required for diagnosis of FAP
- If left untreated, 100% cases progress to colon cancer
- Extra intestinal manifestations like Congenital hypertrophy of retinal pigment epithelium
3. Gardner Syndrome
   FAP + osteoma, epidermal cyst, abnormal dentition
4. Turcot Syndrome
   FAP + Brain tumors [medulloblastoma > Glioblastoma]
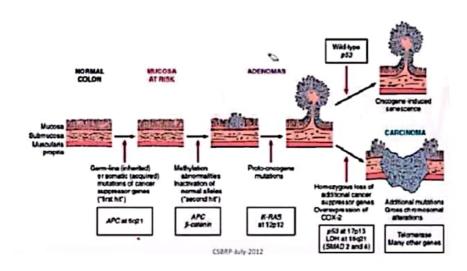
Colon cancer   00:12:05

- Risk factors
  - Smoking
  - Alcohol

Active space

- High fat diet
- Highly processed food
- Less fibre diet
- Inflammatory bowel disease [ulcerative colitis > Crohn's
                                                      disease]
- Protective factor
  -☒ Fish intake
- Genetic factors
  i) FAP → mutation of APC gene on chromosomes 5q21
  ii) HNPCC → mismatch repair gene defect of HMLHI, MSH-1, 2, 6
- Pathogenesis
  Adenocarcinoma sequence [multiple step carcinogenesis]

Normal epithelium ⟶ Epithelium at risk ⟶ Adenoma

       APC gene   K-RAS

                                                     pS3

A — APC GENE
K — K-RAS
S }
3 } - pS3
                                                        ↓
                                                   Carcinoma
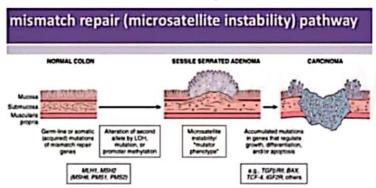
Molecular model for the evolution of colorectal cancers through the adenoma-carcinoma sequence

Active space

– HNPCC

HNPCC[Hereditary non polyposis colon cancer]

mismatch repair (microsatellite instability) pathway

i) Also Known as Lynch Syndrome

ii) ↑ Risk of developing   C   – Colon Cancer

                   E   – Endometrial cancer

                   O   – Ovarian cancer

- microscopy of Colonic Cancer

     Adenocarcinoma [Glands lined by malignant cells]

      – mucinous adenocarcinoma → Signet ring cells are seen

     → Has poor prognosis

- Tumor markers of Colon Cancer

     CA-19-9, CEA (Carcinoembryonic Antigen) in Blood

Active space
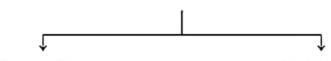
LIVER-NORMAL HISTOLOGY AND CIRRHOSIS

Normal morphology of liver   00:01:22
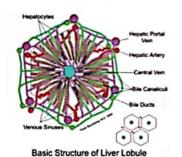
- Weight: 1400 – 1600 gms.
- Lobular architecture.

Hexagonal plates (lobules)

Central vein   Portal triad
                                                  - Bile duct
                                                  - Portal vein
                                                  - Hepatic artery

Basic Structure of Liver Lobule
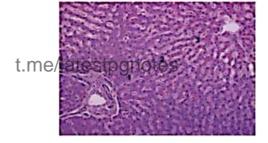
Sinusoids:
region between
rows of hepatocytes

Zones of Liver:

Zone 1 : Periportal zone
Zone 2 : midzonal
Zone 3 : Centrilobular

Zone most susceptible to ischemic damage : Zone 3.
most susceptible to toxin induced damage : Zone 1

Disease affecting each zone:
  mid zonal → Yellow fever
  Periportal → Viral hepatitis
  Centrilobular → Alcohol
         Acetaminophen toxicity
         Chronic venous congestion.
         Ischemia
         Budd Chiari syndrome

Microscopic structure of liver   00:08:06

1. Sinusoids :
- Area between 2 rows of hepatocytes
- Kupffer cells in the lining

→ canal of Hering
○○○○○○○○○
                    - Sinusoids
○○○○○○○○○
Space of Disse
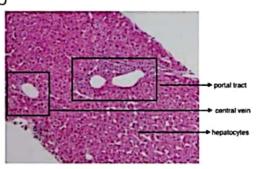
a. Space of Disse

Space between hepatocytes and lining of sinusoids.

Characteristic features :

a) Vitamin A storage
b) Ito cells/stellate cells — fibrosis in cirrhosis.
c) Amyloid first seen in space of Disse.

3. Canals of Hering

- Present between hepatocytes
- Contain oval cells /stem cells of liver

Normal liver biopsy:

- portal tract
- central vein
- hepatocytes
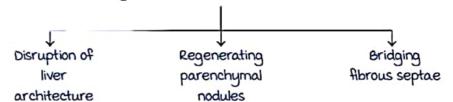
Cirrhosis of liver   00:12:40
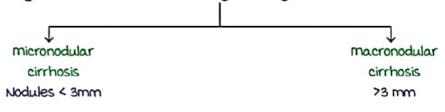
- End stage liver disease
- Characterized by

```
  Disruption of         Regenerating        Bridging
     liver              parenchymal      fibrous septae
  architecture            nodules
```

- Types of cirrhosis — based on regenerating nodules

```
    micronodular                        macronodular
      cirrhosis                            cirrhosis
  Nodules < 3mm                            >3 mm
```

Active space

Causes of micro and macronodular cirrhosis.

micronodular cirrhosis	macronodular cirrhosis
Early ALD	Late ALD
Hemochromatosis	Wilson's disease
1° biliary cirrhosis	α – 1 antitrypsin deficiency Viral
Indian childhood cirrhosis	hepatitis
	Drugs and toxins.

Cirrhosis – pathogenesis and clinical presentation 00:17:09

Causes of cirrhosis:

1. Alcoholic liver disease
2. Non-alcoholic steato hepatitis (NASH)
3. metabolic disorders: α_1 – antitrypsin deficiency
   Wilson's disease
   Hemochromatosis
4. Viral hepatitis
5. Autoimmune hepatitis
6. Drugs and chemicals
7. Biliary diseases

Pathogenesis :

Hallmark : capillarization of sinusoids t.me/latestpgnotes

Normal liver :

   Type 1 and 3 collagen : Periportal and centrilobular area.

   Type 4 collage : space of Disse.

In cirrhosis,
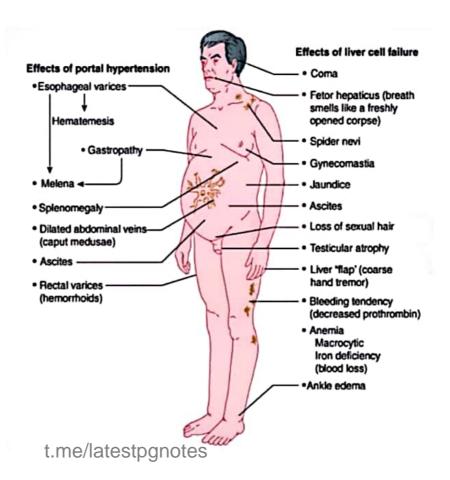
   Type 1 and 3 collagen occupies space of Disse
                    ↓
   Loss of fenestrations of sinusoids
                    ↓
   Capillarization of sinusoids

Active space

Clinical presentation:

Effects of portal hypertension

- Esophageal varices
  ↓
  Hematemesis
  ↓
- Gastropathy
- Melena
- Splenomegaly
- Dilated abdominal veins (caput medusae)
- Ascites
- Rectal varices (hemorrhoids)

Effects of liver cell failure

- Coma
- Fetor hepaticus (breath smells like a freshly opened corpse)
- Spider nevi
- Gynecomastia
- Jaundice
- Ascites
- Loss of sexual hair
- Testicular atrophy
- Liver "flap" (coarse hand tremor)
- Bleeding tendency (decreased prothrombin)
- Anemia
  Macrocytic
  Iron deficiency
  (blood loss)
- Ankle edema

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ALCOHOLIC LIVER DISEASE

Alcoholic liver disease   00:00:08
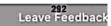
- Alcohol intake of 60-80 ml/day for 10 years — causes alcoholic liver disease
- Gross — soft, yellow, greasy

On Histopathological Examination

Steatosis	Hepatitis	Cirrhosis
• Fatty liver • Reversible • Starts in centrilobular Area (zone-3)	• Hepatocyte swelling • Ballooning degeneration • Neutrophilic infiltrate • mallory hyaline bodies • Some fibrosis seen	• Irreversible • Fibrosis seen

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micro-Vesicular	macro-Vesicular
Small fatty droplet	large fatty droplet

- Laennac cirrhosis — end stage of Alcoholic liver disease
  ↓
  Fibrotic scar

(n) liver   STEATOSIS   MACROVESIC
Microvesic.

Normal liver   steatosis

Active space

MACRO
micro,

Mallory hyaline bodies
00:07:35

- A/K/A. mallory denk bodies
- Composed of — Intermediate filaments-like

↓

CK8, CK18

mallory hyaline bodies

seen in	not seen in
↓	↓

New — Non alcoholic steatohepatitis

Hemochromatosis

Indian — Indian childhood cirrhosis

Primary sclerosing cholangitis

w — Wilson's disease
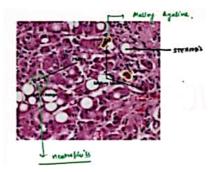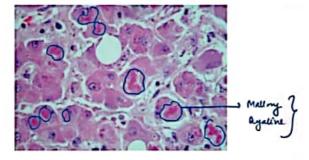
A — Alcoholic liver disease

T — Tumor like hepatocellular carcinoma

C — Primary biliary cirrhosis

H — focal nodular Hyperplasia

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Mallory hyaline.
STRANDS
neutrophils

Mallory hyaline

Active space

Microvesicular steatosis and macrovesicular steatosis   00:11:15

microvesicular steatosis	macrovesicular steatosis
• Acute fatty liver of pregnancy	• Late alcoholic liver diease
• Reye's syndrome	• Obesity
• Early alcoholic liver disease	• Protein energy malnutrition
• Drugs & toxins	• Non alcoholic steatohepatitis (NASH)
	• Chronic hepatitis C

Non alcoholic Steatohepatitis (NASH)

- Features are similar to NASH, no history of alcohol
- Seen in — Obesity
  - metabolic Syndrome
  - Insulin resistance

Alcoholic Steatohepatitis	Non Alcoholic Steatohepatitis
• Mallory hyaline bodies ++	Not present
• Inflammation — more prominent	Less prominent
• Neutrophils predominantly	Macrophages predominantly
• Perisinusoidal > Periportal	Periportal > perisinusoidal

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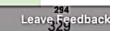
Reye's syndrome   00:15:40

- Rare disorder
- In children suffering from viral illness
  ↓
  Treated with Aspirin
- Due to severe mitochondrial dysfunction
- C/F — rash, vomiting, hypoglycemia, hepatic encephalopathy
- On H & E — Extensive micro vesicular steatosis
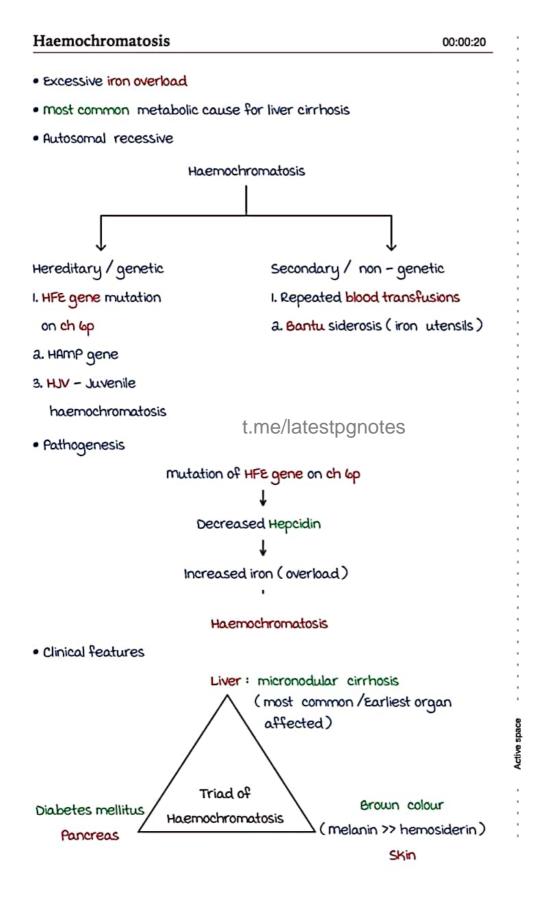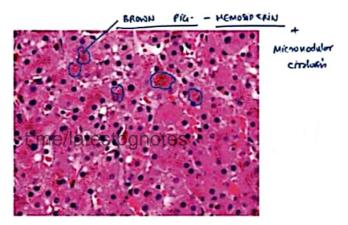
Active space

METABOLIC LIVER DISEASE

Haemochromatosis   00:00:20

- Excessive iron overload

- most common metabolic cause for liver cirrhosis

- Autosomal recessive

```
                    Haemochromatosis
                           |
         ┌─────────────────┴─────────────────┐
         ↓                                   ↓
```

Hereditary / genetic   **Secondary / non - genetic**

I. HFE gene mutation   I. Repeated blood transfusions

   on ch 6p   2. Bantu siderosis (iron utensils)

2. HAMP gene

3. HJV – Juvenile

   haemochromatosis

- Pathogenesis

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<div align="center">

Mutation of HFE gene on ch 6p

↓

Decreased Hepcidin

↓

Increased iron (overload)

Haemochromatosis

</div>

- Clinical features

<div align="center">

Liver : micronodular cirrhosis
(most common /Earliest organ
affected)

</div>

Diabetes mellitus / Triad of \ Brown colour
Pancreas / Haemochromatosis \ (melanin >> hemosiderin)
Skin

- DM + Brown colour → Bronze diabetes
- CVS – restrictive cardiomyopathy

       dilated cardiomyopathy

- Testicular abnormalities gonadal involvement
- Joint involvement
- ↑ risk of hepatocellular carcinoma.
- Lab diagnosis :
  - Blood : S. Iron ↑

        S. Ferritin ↑

        S. Transferrin saturation ↑

        S. TIBC ↓

  - Liver biopsy

BROWN PIG. – HEMOSIDERIN
+
Micronodular cirrhosis

  – Brownish Pigmentation – Hemosiderin

  – Features of micronodular cirrhosis

  – On Prussian blue stain, bluish coloured iron deposits can be seen.

- Treatment :
  - Drug of choice → Fe chelator → Desferoxamine
  - Treatment of choice → Phlebotomy

Active space

Wilson's disease

00:09:39

- Excessive copper accumulation

- Autosomal recessive

- Pathogenesis :

Mutation of ATP7B gene on ch: 13q

↓
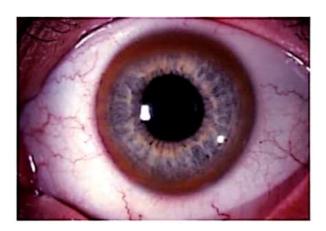
Defect in incorporation of copper into ceruloplasmin

↓

Increased accumulation of copper in tissues

↓

Wilson's disease

- Clinically ──→ Liver →Cirrhosis

→ Eye → Kayser - Fleischer ring

↓

Brownish discolouration in descemet's membrane of cornea.

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→ Brain → Putamen and basal ganglia are affected

↓

Neuropsychiatric manifestations.

- Kayser Fleischer ring :

Active space

- Lab diagnosis : ↑ Copper levels

    ↓ Ceruloplasmin

- Liver biopsy

    - Stain for copper ⟶ Rhodamine

        ⟶ Rubeanic acid

    - Stain for ceruloplasmin ⟶ Orcein

- most sensitive screening test for copper is ↑ urinary excretion of copper.

- Treatment ⟶ Copper chelators

α1 - Antitrypsin deficiency   00:15:50

- Autosomal recessive

- Pathogenesis : deficiency of α1 antitrypsin

    Elastases ⟷ Antielastases (α1 antitrypsin)
    deficiency of α1 antitrypsin
                        ↓
            ↑ Elastase activity
                        |
         ┌──────────────┴──────────────┐
       Lung   Liver
    panacinar emphysema   cirrhosis

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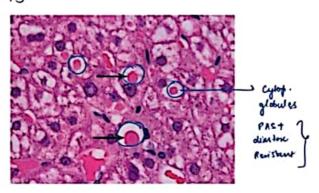
- Genetics

    Pi mm ⟶ normal

    Pi mz ⟶ heterozygous

    Pi ZZ ⟶ α1 deficiency

- On microscopy :

Cytop. globules
PAS+
diastase Resistant

1. Steatosis

2. Cytoplasmic globules : PAS ⊕
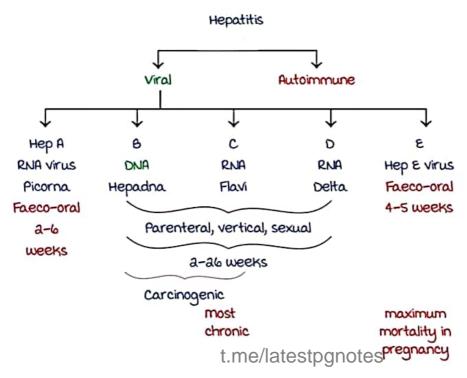
    Diastase resistant

    periportal area

HEPATITIS
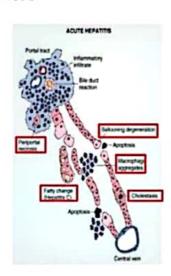
- Hepatitis is inflammation of Liver parenchyma

Hepatitis

├── Viral
│   ├── Hep A — RNA virus — Picorna — Faeco-oral — 2-6 weeks
│   ├── B — DNA — Hepadna — Parenteral, vertical, sexual — 2-26 weeks — Carcinogenic
│   ├── C — RNA — Flavi — most chronic
│   ├── D — RNA — Delta
│   └── E — Hep E virus — Faeco-oral — 4-5 weeks — maximum mortality in pregnancy
└── Autoimmune

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Acute hepatitis   00:03:40

- morphology of acute hepatitis
  - Ballooning degeneration: swelling of hepatocytes
  - Disruption of lobular architecture
  - Inflammation
  - Spotty necrosis
  - Councilman bodies — Apoptotic bodies
  - Absence of portal inflammation
  - Central — portal brigding necrosis
  - Drop out of hepatocytes
- Acute Hepatitis

Active space

- Balloon degeneration
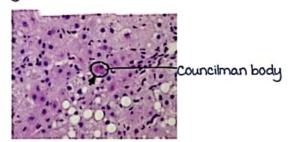
Balloon degeneration

- Councilman body
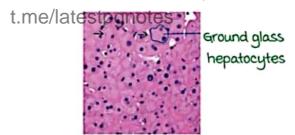
Councilman body
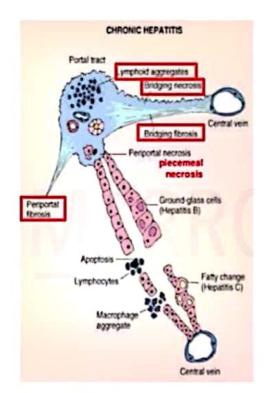
Chronic hepatitis   00:07:40

- morphology
  - Ground glass hepatocytes : seen in Hep B infection due to deposition of surface antigens.

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Ground glass hepatocytes

- Bridging Fibrosis : bridged between the central vein and portal tract.
- Mononuclear portal inflammation
- Interface hepatitis
- Cirrhosis

Active space

CHRONIC HEPATITIS
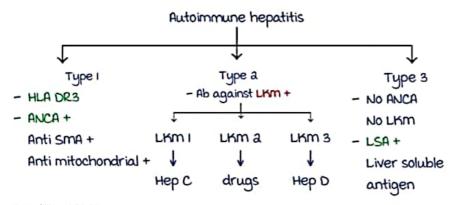
- microscopy of Hep C infection :
  - Steatosis : fatty change
  - Lymphoid aggregates
  - Bile duct damage and proliferation

Autoimmune hepatitis

- Females > males

Type 1	Type 2	Type 3
- HLA DR3	- Ab against LKM +	- No ANCA
- ANCA +		No LKM
Anti SMA +	LKM 1 LKM 2 LKM 3	- LSA +
Anti mitochondrial +	↓ ↓ ↓	Liver soluble
	Hep C drugs Hep D	antigen
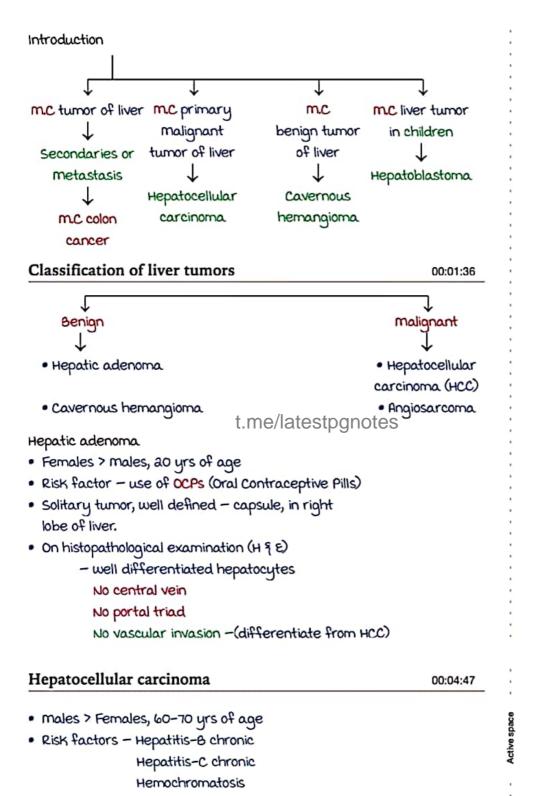
- microscopy:
  - ↑ Plasma cells infiltration
  - Hepatic Rosettes
  - Emperipolesis
  - Interface hepatitis

HEPATIC TUMORS AND BILE DUCT DISORDERS

Introduction

- m.c tumor of liver → Secondaries or metastasis → m.c colon cancer
- m.c primary malignant tumor of liver → Hepatocellular carcinoma
- m.c benign tumor of liver → Cavernous hemangioma
- m.c liver tumor in children → Hepatoblastoma

Classification of liver tumors   00:01:36

Benign
- Hepatic adenoma
- Cavernous hemangioma

Malignant
- Hepatocellular carcinoma (HCC)
- Angiosarcoma

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Hepatic adenoma
- Females > males, 20 yrs of age
- Risk factor — use of OCPs (Oral Contraceptive Pills)
- Solitary tumor, well defined — capsule, in right lobe of liver.
- On histopathological examination (H & E)
    - well differentiated hepatocytes
        No central vein
        No portal triad
        No vascular invasion —(differentiate from HCC)

Hepatocellular carcinoma   00:04:47

- males > Females, 60-70 yrs of age
- Risk factors — Hepatitis-B chronic
    Hepatitis-C chronic
    Hemochromatosis
    Tyrosinemia
    Alcohol
    Aflatoxin
    Non alcoholic steatohepatitis

Active space
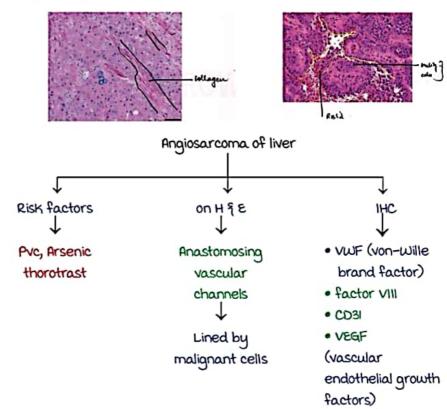
- Pre neoplastic conditions for development of HCC
↓

Hepatic adenoma
Small cell dysplastic nodule
Large cell dysplastic nodule

- morphology — multifocal tumor
Angioinvasive
Mallory Hyaline bodies seen
Cord & sheets & trabeculae of cells

- Immunohistochemical markers (IHC) — Alpha fetoprotein (AFP)
Hep Par – 1
Neurotensin
Glypican – 3

Fibrolamellar variant of hepatocellular carcinoma   00:08:43
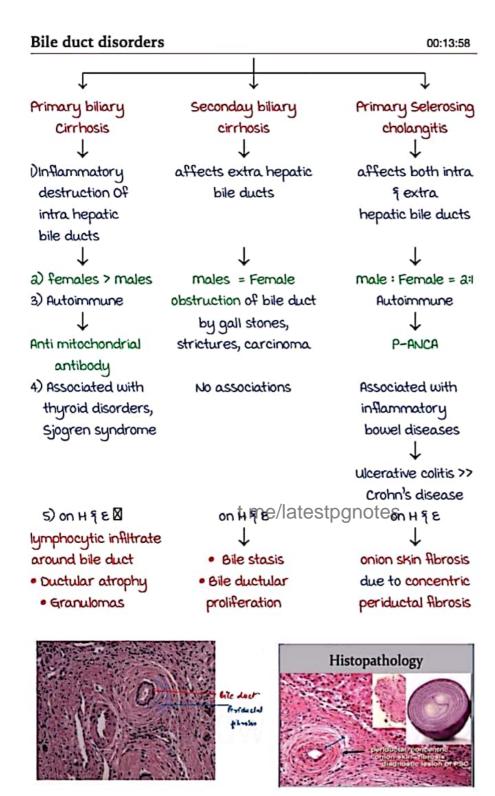
- male = Females
- Not associated with Hepatitis B, C
↑ AFP (Alpha feto protein)
- Better prognosis
- Spreads by lymphatic route
- On H & E — Abundant collagen
Abundant fibrosis — stained by — masson's trichrome
- IHC markers — Neurotensin

collagen

Angiosarcoma of liver

Risk factors	on H & E	IHC
↓	↓	↓
Pvc, Arsenic thorotrast	Anastomosing vascular channels ↓ Lined by malignant cells	• VWF (von-Wille brand factor) • factor VIII • CD31 • VEGF (vascular endothelial growth factors)

Active space

Bile duct disorders

00:13:58

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                          │
        ┌─────────────────┼─────────────────┐
        ↓                 ↓                 ↓
```

Primary biliary Cirrhosis	Seconday biliary cirrhosis	Primary Selerosing cholangitis
↓	↓	↓
1)Inflammatory destruction Of intra hepatic bile ducts	affects extra hepatic bile ducts	affects both intra & extra hepatic bile ducts
↓	↓	↓
2) females > males	males = Female	male : Female = 2:1
3) Autoimmune ↓ Anti mitochondrial antibody	obstruction of bile duct by gall stones, strictures, carcinoma	Autoimmune ↓ P-ANCA
4) Associated with thyroid disorders, Sjogren syndrome	No associations	Associated with inflammatory bowel diseases ↓ Ulcerative colitis >> Crohn's disease
5) on H & E lymphocytic infiltrate around bile duct • Ductular atrophy • Granulomas	on H & E ↓ • Bile stasis • Bile ductular proliferation	on H & E ↓ onion skin fibrosis due to concentric periductal fibrosis

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bile duct
Periductal fibrosis

Onion skin fibrosis

Histopathology

periductal concentric onion-skin fibrosis diagnostic lesion of PSC

Onion skins in medicine

- H & E — Primary sclerosing cholangitis

- In X-ray — Ewing's sarcoma

- H & E — Hyperplastic arteriosclerosis

- Nerve biopsy — Chronic inflammatory demyelinating polyneuropathy
- Spleen in systemic lupus erythematosus
- Electron microscopy of Tay sachs disease
- Myelin figures

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Active space

KIDNEY - BASICS

Urine microscopy/examination   00:01:41
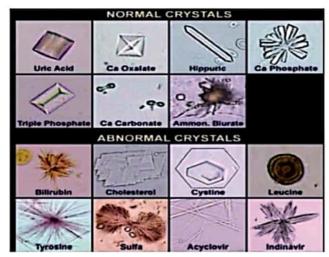
Examination of : Cells
                 Casts
                 Crystals
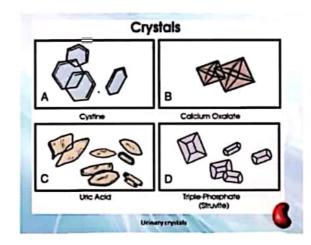
1. Casts:
   1) All casts are composed of Tamm Horsefall protein
   2) Produced in thick ascending limb of loop of Henle.

Cast	Condition
1. Hyaline cast	Normal individual, Fever, Exercise, Dehydration, Stress
2. RBC cast	Glomerulonephritis
3. WBC cast	Pyelonephritis
4. Broad/Waxy cast	Chronic Renal Failure (CRF)
5. Lipid/Fatty cast	Nephrotic syndrome
6. muddy brown granular cast	Acute Tubular Necrosis (ATN)

2. Crystals

NORMAL CRYSTALS
Uric Acid | Ca Oxalate | Hippuric | Ca Phosphate
Triple Phosphate | Ca Carbonate | Ammon. Biurate
ABNORMAL CRYSTALS
Bilirubin | Cholesterol | Cystine | Leucine
Tyrosine | Sulfa | Acyclovir | Indinavir

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Crystals

A. Cystine
B. Calcium Oxalate
C. Uric Acid
D. Triple-Phosphate (Struvite)

Urinary crystals
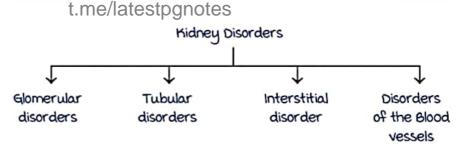
- Calcium crystals
  - Calcium oxalate — Envelope shaped
  - Calcium carbonate — Dumbbell shaped
- Cystine crystal : Hexagonal shape

- Triple phosphate crystal (struvite) : Coffin lid shaped

Warning : Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with marrow Edition 4 videos.

Structure of glomeruli   00:09:26

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```
              Kidney Disorders
                     |
  ┌──────────┬───────┴───────┬──────────────┐
  ↓          ↓               ↓              ↓
Glomerular  Tubular      Interstitial   Disorders
disorders   disorders    disorder       of the Blood
                                         vessels
```
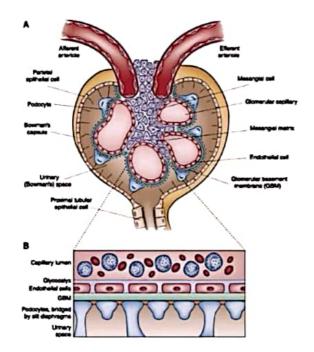
Glomeruli — Structure

a.   2 layers of epithelial cells
```
         ┌───────────────┴───────────────┐
         ↓                               ↓
      Parietal                        Visceral
                                  (has podocytes)
```
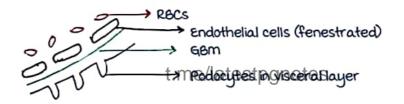
b. mesangial cells
   - phagocytic cells
   - Capable of proliferation

c. Glomerular basement membrane (GBM)
   - Composed of Type IV collagen

Active space

A

B

d. Filtration membrane

→ RBCs
→ Endothelial cells (fenestrated)
→ GBM
→ Podocytes in visceral layer
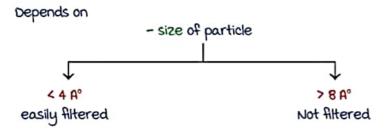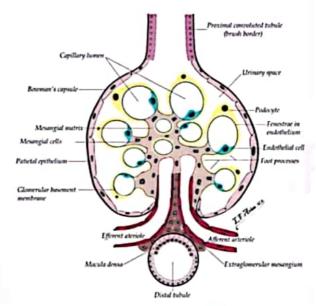
e. Bowman's space:
Space between visceral and parietal epithelium

Filtration process

Depends on

- size of particle

< 4 A°
easily filtered

> 8 A°
Not filtered
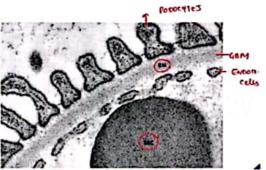
- Charge of particle
Repels all the substances that are negatively charged

Active space

Electron microscopy
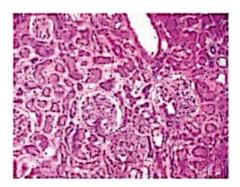
Kidney biopsy   00:18:37

- A minimum of 10 glomeruli are required to study a kidney biopsy slide.

Normal kidney biopsy

- Provides information about
  - Lesion in Glomeruli
  - Tubules
  - Interstitium
  - Vessels

Active space
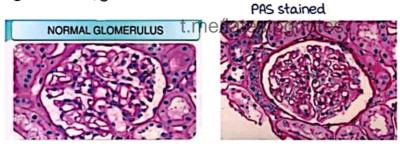
Lesions in a glomeruli :

I. Proliferative disease
  - ↑ Cellularity
  - Proliferation of epithelial cells, mesangial cells, leukocytes

a. Focal
  < 50% glomeruli are affected

3. Segmental
  A portion of the glomeruli is affected

4. Global
  The entire glomeruli is affected.

5. Diffuse
  > 50% glomeruli are affected.

Kidney Biopsy
  a) Light microscopy
  b) Electron microscopy
  c) Immunofluorescence

Light microscopy

PAS stained
NORMAL GLOMERULUS

- Normal glomerulus on a light microscopy
  - Only 1 or 2 cells per capillary tuft
  - Capillary lumens are open
  - Thickness of glomerular capillary wall is similar to the tubular basement membrane.
  - mesangial cells are located in centre/stalk of the tuft.
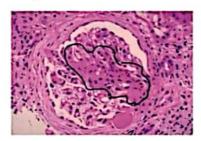
Stains used
  - PAS stain
  - Reticulin/Silver stain
  - Congo red stain (Amyloid)
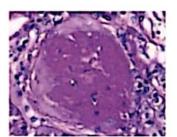
Abnormal glomerulus

The above picture shows:
- Capillary lumen – closed
- ↑ cellularity
- Amyloid/sclerosis (more common)

Segmental Sclerosis
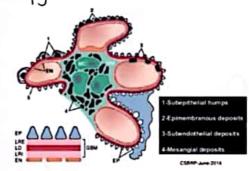
Global Sclerosis

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Kidney biopsy - electron microscopy & immunofluorescence

00:29:55

Electron microscopy

1-Subepithelial humps
2-Epimembranous deposits
3-Subendothelial deposits
4-Mesangial deposits
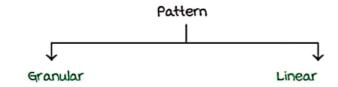
Deposits	Conditions
I. Subepithelial Deposits	• Post Streptococcal glomerulonephritis (PSGN) • Rapidly progressive glomerulonephritis (RPGN) • membranous glomerulonephritis

Active space
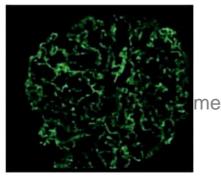
2. Subepithelial deposits
    - membranoproliferative Glomerulonephritis (mPGN)-I
    - Lupus Nephritis
3. Intramembanous deposits
    - mPGN – II
4. mesangial deposits
    - Henoch – Schonlein Purpura (HSP)
    - IgA Nephropathy

Immunofluorescence

```
                    Pattern
                       |
        ┌──────────────┴──────────────┐
        ↓                             ↓
    Granular                       Linear
```
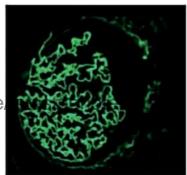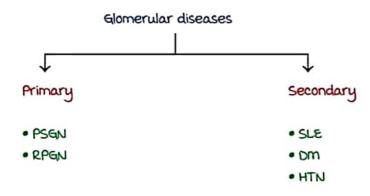
Seen in Immune complex,   Basement membrane disease
Complement deposition   ↓
                                   Goodpasture syndrome

Active space

GLOMERULAR DISEASES - NEPHRITIC

Glomerular diseases

Primary

• PSGN
• RPGN

Secondary

• SLE
• DM
• HTN

Clinically manifest in 2 forms:

Nephrotic Syndrome

• massive proteinuria
  (>3.5 gm / 24 hr)
• Hypoalbuminemia
• Edema
• Hyperlipidemia
• Lipiduria – Fatty
  casts in urine
• Coagulopathies
• Seen in : – minimal change
            disease (MCD)
  – Focal segmental
  glomerulosclerosis (FSGs)
  – membranous
  glomerulopathy
  – membrane proliferative
  glomerulo nephritis (mPGN)
  –IgA nephropathy

Nephritic Syndrome

• Proteinuria
  (<3.5 gm / 24 hr)
• Edema
• Hematuria
• Hypertension
• Azotemia
• Seen in:
  – Post Streptococcal Glomerulo
    nephritis (PSGN)
  – Rapidly progressive
    Glomerulo nephritis (RPGN)
  – mPGN
  – Goodpasture's Syndrome
  – Alport Syndrome
  – Thin Basement membrane
    disease
  –IgA nephropathy

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Post Streptococcal Glomerulo Nephritis   00:06:08

- Type III hypersensitivity reaction
- Immune complex mediated
- 5-15 yr Age
- 2-4 weeks after Streptococcal sore throat infection

$$\downarrow$$
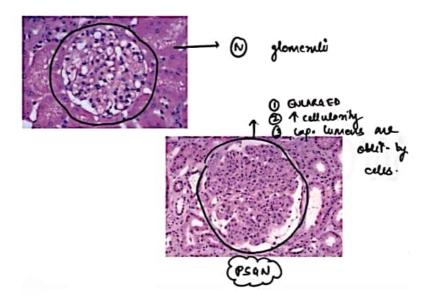
Strains 12, 4, 1

- Clinically: Cola coloured urine, edema, hematuria
- microscopy:

  • Light microscopy (Lm) : - Enlarged hypercellular glomeruli
                            - ↑ Cellularity by leucocytes
                            - Endo & Exocapillary proliferation
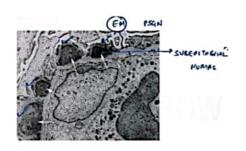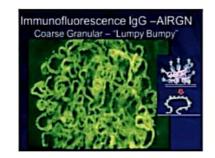
  • Electron microscopy (Em) : - subepithelial humps

                              $$\downarrow$$

                              Due to immune complex deposition

  • Immunofluorescence (IF) : - Granular appearance (lumpy
                                bumpy deposition)

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→ (N) glomeruli

① Gulara ed
② ↑ cellularity
③ cap. lumens are
    obleit- by
    cells.

(PSGN)

Active space

EM   PSGN
→ SUBEPITHELIAL HUMAP

Immunofluorescence IgG –AIRGN
Coarse Granular – "Lumpy Bumpy"
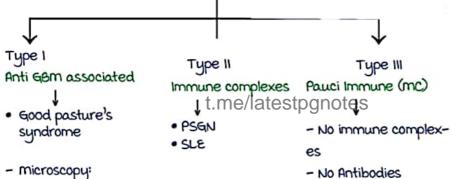
- most cases resolve spontaneously

- 1% of case – RPGN

Rapidly progressive glomerulonephritis   00:13:50
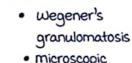
- A/k/a – Cresentric glomerulo nephritis

- Types:

Type I Anti GBM associated	Type II Immune complexes	Type III Pauci Immune (mc)
• Good pasture's syndrome	• PSGN • SLE	– No immune complex-es
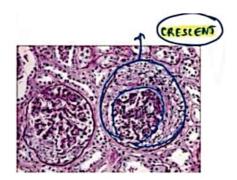
– microscopy:
  • Light microscopy : > 50% of glomeruli will show crescents.
  – It is formed by proliferation of
    • Parietal epithelial cells
    • Fibrin
    • Leucocytes
  – ↑ Number of crescent, poorer is the prognosis
		– No Antibodies
		    • Wegener's granulomatosis
		    • microscopic Polyangitis
		  – Best Prognosis

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CRESCENT

Active space
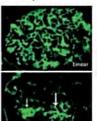
- Electron microscopy:
- Rupture of Glomerular basement membrane

- Immunofluorescence

- Type I → Linear pattern
- Type II → Granular deposits
- Type III → No deposits

Crescentic glomerulonephritis (Rapidly progressive)

- IF:
  1. Type I : Linear IgG and C3 staining of GBM. Fibrin positive in areas of necrosis, crescents, periglomerular interstitium, and in Bowman's capsules
  2. Type II : Granular immune deposits of variable immunoglobulins and complement components (mesangial, capillary loops)
  3. Type III : Negative or very weak staining, fibrin positivity in glomerular necrosis, cellular crescents and in fibrinoid vascular necrosis

Goodpasture syndrome   00:23:35

1 → Type I RPGN
2 → Type II Hypersensitivity Reaction
        ↓
     Anti GBM antibodies
3 → Defect α3 chain of collagen type IV
4 → Collagen type IV defect
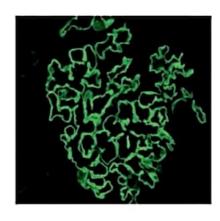
- Clinical features:
  - Lung : Hemoptysis (mc & earliest)
  - Kidney : hematuria
  mcc of death = Renal disease

- LM : Crescents
- EM : Rupture of GBM
- IF : linear pattern
        ↓
    Smooth deposition

IgA nephropathy   00:24:45

- AKA Berger's disease
- mc type of glomerulonephritis in adults-world wide
- mcc of gross & recurrent hematuria.
- Pathogenesis : ↑ mucosal secretion of IgA1

- microscopy : • LM = – mesangial widening
            – Deposition of IgA in mesangium

        • EM = mesangial deposits

        • IF = mesangial deposits of IgA, C3, Properdin

PSGN	IgA Nephropathy
– Children	– Adults
– Hematuria occurs 10-14 days after sore throat	– 2-4 days after sore throat/GI infection

Alport syndrome   00:31:28

- Hereditary nephritis
- Follows all modes of Inheritance
- MC mode of Inheritance – X-linked dominant
- Clinically: (Triad) → mnemonic – "Can't see, Can't pee, Can't hear a Buzzing Bee"

        ├── Anterior lenticonus = Eye
        ├── Hematuria = Kidney → MC affected & earliest manifestation
        └── Sensorineural deafness = Ear – MC extra renal organ affected

- Pathogenesis: mutation in α5 chain of collagen type IV
    - Only diagnosed by Electron microscopy
            ↓
    Basket weave appearance
    Thinning of Basement membrane
    (earliest lesion) ↓
    Basement membrane thinning & lamination of Lamina densa
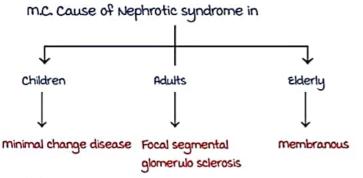
Thin basement membrane disease   00:37:00

- A/K/a – Benign familial hematuria
- Normal thickness of Basement Membrane – 300-400nm
- Basement membrane thickness decreased to 155 – 200 nm
- Due to mutation of α4 chain of collagen type IV

Active space

GLOMERULAR DISEASES: NEPHROTIC

m.c. Cause of Nephrotic syndrome in

Children	Adults	Elderly
↓	↓	↓
minimal change disease	Focal segmental glomerulo sclerosis	membranous

Minimal change disease   00:01:53

- Age of presentation – 2-6 yrs
- A/k/a Lipoid nephrosis / Nil deposit disease
- Idiopathic.

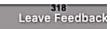microscopy:

1. LM – No change in glomeruli

   Lipid in tubules → Lipoid Nephrosis.

2. EM – Diffuse effacement of podocyte foot process – Podocytopathy

EM – MCD
Podocyte foot process effacement
(a) normal
Podocyte
BM
endoH
(b) effacement

3. Immunofluorescence – No deposits → Nil deposit disease
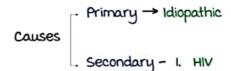
Clinically – Selective proteinuria → ∴ respond to steroids.

Active space
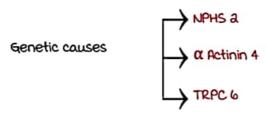
Focal segmental glomerulosclerosis (FSGS)

00:06:46

m.c. in adults.

Causes
- Primary → Idiopathic
- Secondary –
  1. HIV
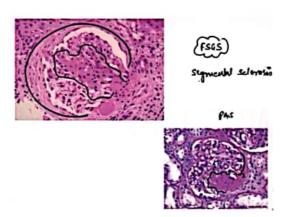 2. Renal ablation surgery
  3. Sickle cell anemia
  4. Reflux nephropathy
  5. Heroin addiction
  6. Hypertension
  7. IgA nephropathy
  8. Obesity

Genetic causes
→ NPHS 2
→ α Actinin 4
→ TRPC 6

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microscopy:

1] LM → <50% glomeruli show segmental sclerosis.

FSGS
Segmental sclerosis

PAS

a] LM → Diffuse effacement of podocyte foot processes.

3] IF – Ig & C3 deposition in sclerotic area

Variants

1. FSGS – NOS (not otherwise specified) → m.c.

2. Collapsing variant → worst prognosis
                        associated with HIV

3. Perihilar variant

4. Cellular variant

5. Glomerular tip variant → Best prognosis

Warning : Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with marrow Edition 4 videos.

Genetic basis of nephrotic syndrome   00:14:07

① NPHS I

- Gene on 19q chromosome
- Encodes for Nephrin
- Responsible for congenital nephrotic syndrome of Finnish type

② NPHS 2
- Gene on 19q chromosome
- Encodes for podocin
- Responsible for steroid resistant nephrotic syndrome, FSGS

③ α – Actinin 4
- Podocyte actin binding protein
- Adult onset – FSGS

④ TRPC 6 (Transient receptor protein channel 6)
- Adult onset FSGS

Active space

Membranous nephropathy   00:18:01

- m.c.Cause of nephrotic syndrome in elderly

- Causes - 1] Idiopathic

   2] Renal vein thrombosis

   3] malignancy → Ca. Colon

                        Ca. Lung

   4] Infections →   malaria, Syphilis, Leprosy

                        Hep B, Hep C

                        Schistosomiasis

   5] SLE

   6] Drugs → NSAIDs, Penicillamine

Pathology : Immune complex mediated

   HLA - DR1

   antibodies against PLA2 receptors (Phospholipase A 2)

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microscopy

   1] Lm - Diffuse thickening of Glomerular basement membrane

(immune complex deposition) on silver stain → Spike & dome

appearance.

Spike   Immune
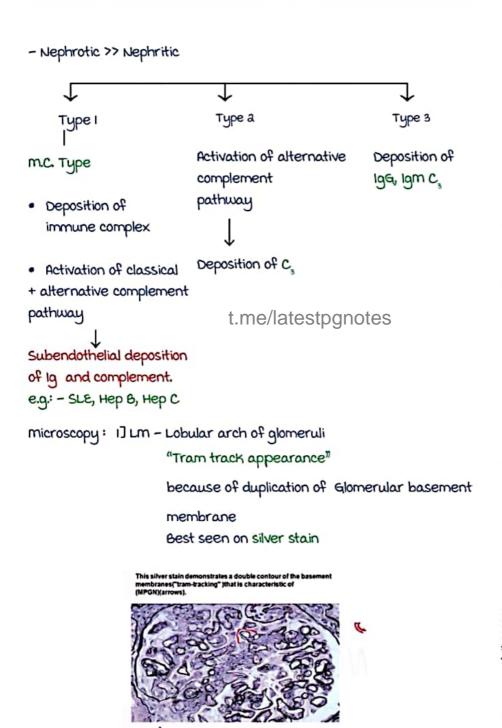   complex (Dome)
|
Elaboration of BM material

LIGHT MICROSCOPY

Uniform, diffuse thickening of the glomerular capillary wall.
Basement membrane material is laid down between these deposits, appearing as
irregular spikes protruding from the GBM.
These spikes are best seen by silver stains, which color the basement membrane black.

Marked diffuse thickening of the capillary walls without an increase in the
number of cells. There are prominent spikes projecting from basement
membrane.

silver stain

a] IF → Granular deposits.

3] EM → Subepithelial deposits.

effacement of podocyte foot processes.

Membranoproliferative glomerulonephritis (MPGN)   00:25:25

- Nephrotic >> Nephritic

Type I	Type 2	Type 3

Type I

m.C. Type

- Deposition of
  immune complex

- Activation of classical
+ alternative complement
pathway
↓
Subendothelial deposition
of Ig and complement.
e.g.: - SLE, Hep B, Hep C

Type 2

Activation of alternative
complement
pathway
↓
Deposition of C₃

Deposition of C_3

Type 3

Deposition of
IgG, IgM C_3

microscopy : 1] LM – Lobular arch of glomeruli

"Tram track appearance"

because of duplication of Glomerular basement

membrane

Best seen on silver stain

This silver stain demonstrates a double contour of the basement
membranes("tram-tracking")that is characteristic of
(MPGN)(arrows).

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Active space

a] IF →   Type I – Subendothelial deposits.

                Type 2 – Intramembranous deposits.

                Dense deposit disease – ∵ of C3 deposits.

Active space

a] IF →   Type I – Subendothelial deposits.

                Type 2 – Intramembranous deposits.

RENAL INVOLVEMENT IN SYSTEMIC DISEASE

Diabetic nephropathy   00:00:27

- Risk ↑ with ↑ duration of the disease

- Type I > Type II

- microscopy:

  • Thickening of GBM (Earliest)   + Tubular Basement membrane

  • Diffuse Glomerulosclerosis
    (mc histologic abnormality)

  • Nodular Glomerulosclerosis   – Kimmelsteil wilson Lesion
    (most specific finding)   ↓

  • Renal papillary nercosis   PAS +

  • Fibrin caps   Capsular Drops
         ↓   ↓
    ↑ Hyaline deposition in   ↑ hyaline in Bowman's Capsule
    glomerular capillaries
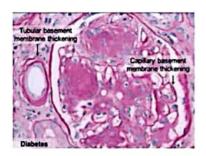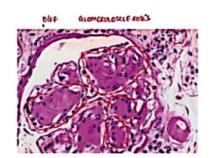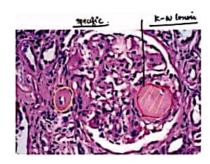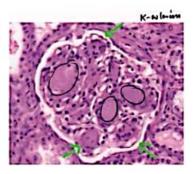
  • Armani ebstein lesion   → uncontrolled/poorly controlled DM
         ↓
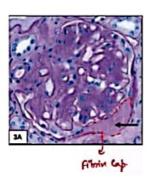
Development of cytoplasmic
vacuoles in PCT due to glycogen

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Tubular basement membrane thickening / Capillary basement membrane thickening / Diabetes

DIFF   GLOMERULOSCLEROSIS

specific :   K-W lesion

K-W lesion

Active space

CAPSULAR DROPS

Fibrin Cap

ARMANI EBSTEIN   GLYCOGEN

P.T.

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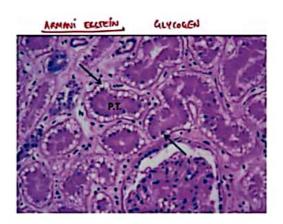
Renal Papillary Necrosis: Causes

    S – Sickle cell anaemia

) – Obstructive uropathy

    D – DM (mc cause)

    A – analgesic use

Lupus nephritis

– WHO Grading: I – minimal mesangial
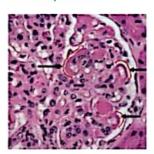
                  II – mesangio proliferative

                  III – Focal proliferative

                  IV – Diffuse proliferative → mc

                  V – membranous

                  Iv – Dense sclerosing

Class IV → wire loop lesion ⊕ [also seen in class III & V]

Active space

Hypertensive nephropathy

00:12:42

Types ┬ Benign nephrosclerosis
      └ malignant nephrosclerosis
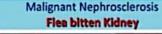
– Benign nephrosclerosis:
Grossly: Leather grain
          appearance

• microscopy: Hyaline
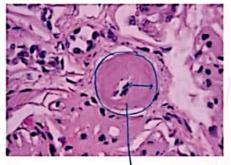 arteriosclerosis

– malignant nephrosclerosis:
– Flea bitten Kidney
(Petechial hemorrhages
rupture of capillaries)

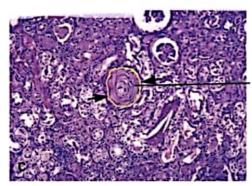• Hyperplastic Arteriosclerosis

↓

Onion skin lesions

Malignant Nephrosclerosis
Flea bitten Kidney

↓ HYALINE ARTERIOSC.

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Onion skin appearance

Causes of Flea bitten Kidney :   – malignant hypertension
                                 –RPGN
                                 –SLE
                                 –Sub acute bacterial endocarditis
                                 –Polyarteritis nodosa
                                 –Henoch Schonlein purpura

Active space

Causes of Onion skin appearance in medicine:

- Histopathology of malignant hypertension
- Nerve biopsy in Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
- X-ray of Ewings sarcoma
- Spleen in SLE
- EM in Tay sachs disease
- Histopathology of 1° sclerosing cholangitis

Chronic glomerulonephritis   00:18:50

- Cause: • RPGN (mcc)
          • PSGN
          • membranous, MPGN
- Grossly: Symmetrically contracted kidney, Granular surface
- Histopathology: - Glomeruli replaced by sclerosis
                   - Tubular atrophy
                   - Interstitial inflammation

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Active space

KIDNEY-TUMORS

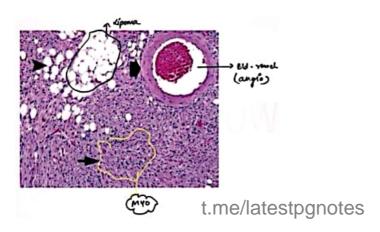## Benign tumors   00:00:27

- Renal papillary adenoma:
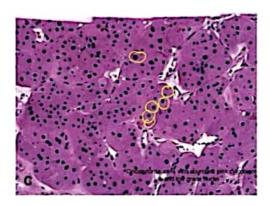 - Presents as yellow plaques
  - Histologically → Papillary tissue

- Angio- myolipoma:
  - Histology : vessel, muscle, fat
  - associated with tuberous sclerosis

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- Oncocytoma:
  - Arises from intercalated cells of the collecting duct
  - epithelial cell malignancy
  - grossly : Tan mahogany brown tumor
  - Histopathology : cells with abundant eosinophilic granular
                     cytoplasm (due to excess of mitochondria)
  - Electron microscopy-Numerous mitchondrias

Active space

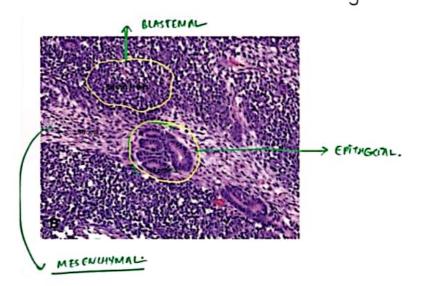## Malignant Tumor: in children

00:05:49

Wilm's tumor:

- Age → 2-5 yr
- mc 1° renal tumor of childhood
- A/K/a Nephroblastoma
- usually presents as an abdominal mass
- Pathogenesis : loss of function mutation in tumor suppressor

Gene → WT 1 – chromosome 11p13

WT 2 – chromosome 11p15

- Associated syndromes:
  - WAGR – wilms tumor, aniridia, genital abnormalities, mental retardation.
  - Denys Drash
  - Beckwith Wiedeman – Adrenal cytomegaly hemihypertrophy
- Histopathology : Triphasic pattern

Epithelial	mesenchymal	Blastemal
• Glands	• Spindle cells	• Dark blue primitive looking cells
• Rosette		

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most important prognostic

Factor ⟶ Histologic anaplasia

Active space

- Precursor -   Nephrogenic cell rests

Malignant tumor: In adults   00:12:04

- Renal cell carcinoma (RCC)
  • ♂ >> ♀
  • Age-6th or 7th decade
  • AKa - Grawitz tumor, adenocarcinoma, Hypernephroma
  • Risk factor : smoking, obesity, petroleum product, asbestos,
          chronic kidney disease, dialysis, hypertension,
          tuberous sclerosis
  • RCC ⎰ Sporadic(mc)
         ⎱ Familial

  • Genetic basis- • VHL gene (von Hippel Landau)
          - gene on ch.3p
          - Autosomal dominant
          - ↑ Risk of clear cell RCC
       • HL RCC (hereditary leiomyomatosis
              renal cell carcinoma)
          - mutation in fumarate hydratase gene
          - Associated with paplillary RCC
       • HP RCC (hereditary papillary RCC)
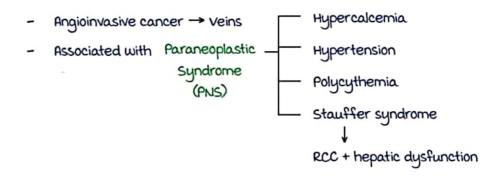   - mutation in MET proto oncogene
                      ↓
              Hepatocyte growth gene
                  (Scatter factor)
       • Birt Hogg Dube syndrome
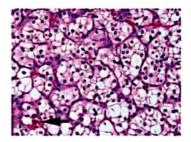   - mutation of BHD gene
                      ↓
                  Folliculin
          - ↑ risk of chromophobe RCC

Active space

– Loss of y chromosome ⎫
– Hypodiploidy   ⎬ Other genetic abnormality
– Trisomy 7, 17   ⎭

– Clinical features : (Triad) ⟨ Hematuria (mc & earliest)
                                  Abdominal mass
                                  Flank pain

– Angioinvasive cancer → Veins
– Associated with Paraneoplastic Syndrome (PNS) ⟨ Hypercalcemia
                                                   Hypertension
                                                   Polycythemia
                                                   Stauffer syndrome
                                                      ↓
                                              RCC + hepatic dysfunction

– MC PNS associated with RCC → ↑ ESR
– mc site of RCC metastasis – lung

Types of RCC   00:20:55

• clear cell RCC:

  – mc type of RCC
  – Solitary unilateral
  – Genetic: VHL on chromosome 2 mutation
  – usually arise from proximal tubules
  – microscopy :

    • Polygonal cells with clear cytoplasm (PAS +)
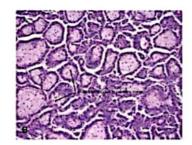   • Oil red O +

  – Immunohistochemical markers(IHC)

        vimentin → +
        (cytokeratin)

Active space

- Papillary RCC:
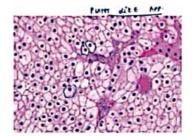 - and mc RCC → 10-15% cases
  - arises from either PCT/DCT
  - genetic: Type I - HP - RCC
            Type 2 - HL - RCC
            - loss of Y chromosome, trisomy 7,17
  - multifocal, bilateral, associated with dialysis
  - Histopathology: Papillae - core filled with foamy histiocytes with psamomma bodies
  - Psamomma bodies: foci of Dystrophic calcification
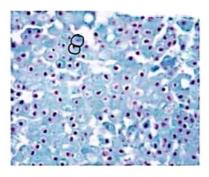   Seen in: Papillary thyroid ca, Papillary RCC, meningioma, Serous cystadenocarcinomas

  - IHC: CK -7 +

- Chromophobe RCC:
  - Arise from intercalated cells of collecting duct
  - genetics: Birt Hogg Dube syndrome, hypodiploidy
  - microscopically: pale eosinophilic cells, perinuclear halo,
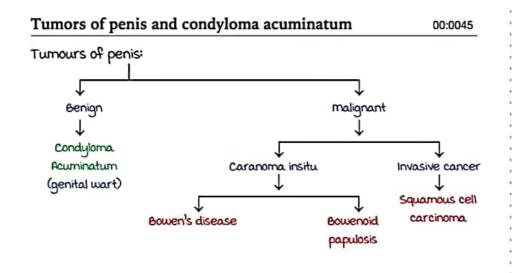   Resin like nucleus → plant like appearance

  - IHC: CK -7 ⊕
    - Best prognosis
    - special stain: Hale's colloidal Iron

- Collecting duct/Bellini duct RCC:

  - Least common RCC

  - Worst prognosis

  - Arises from collecting duct cells in medulla

  - microscopically : hobnail cells, extensive desmoplasia

- medullary RCC:

  - Associated with sickle cell trait

  - Arises from collecting duct cells

- Xp 11.2 RCC:

  - Associated with childhood RCC

  - Genetics : TFT gene mutation on chr Xp11.2

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Active space

MALE GENITAL SYSTEM - PENIS

Tumors of penis and condyloma acuminatum   00:0045

Tumours of penis:

- Benign
  - Condyloma Acuminatum (genital wart)
- Malignant
  - Caranoma insitu
    - Bowen's disease
    - Bowenoid papulosis
  - Invasive cancer
    - Squamous cell carcinoma

Condyloma acuminatum:

→ Genital warts
→ Caused by low Risk HPV 6,11
→ Lesion seen on glans and inner surface of prepuce
→ clinically
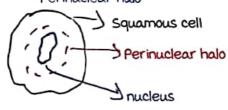   Red velvety excrescence
→ Histopathology:
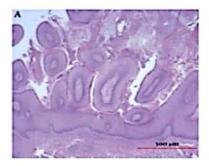   - Branching, villous, papillary connective tissue stroma.

Epithelium → Acanthosis
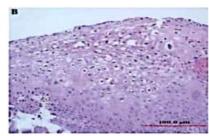   → Hyperkeratosis

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Koilocytic change:

Cells with-
   - Thick membrane
   - Resin like nucleus
   - Perinuclear halo

   → Squamous cell
   → Perinuclear halo
   → nucleus

Active space

Bowen's disease and bowenoid papulosis 00:07:12

Bowen	Bowenoid
Elderly	35 yrs, sexually active
Solitary	multiple lesion
10% risk for squamous cell Carcinoma	Low risk of transformation to SCC → Spontaneously regress

Squamous cell carcinoma of penis 00:09:07

→ Age – 40-50 yrs
→ Associated with poor genital
   hygiene, high risk HPV (HPV 16, 18)
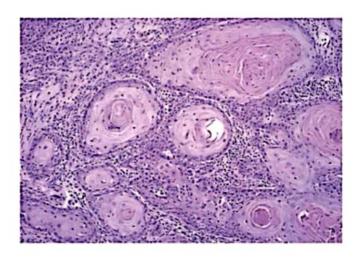→ Affects glans and shaft of penis.

Histopathology:

- Keratin pearls
- Desmosomes (Inter
  bridging between two cells)

IHC:- Cytokeratin
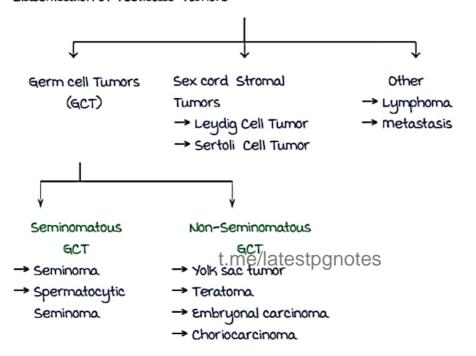- Keratin pearls seen in well differentiated SCC

Squamous cell carcinoma

Active space

TESTICULAR TUMORS

Introduction   00:00:30

Normal Histology of testis
- Sperms are contained in Seminiferous tubules
- Interstitial tissue : has Leydig cells.

Classification of Testicular Tumors

Germ cell Tumors (GCT)	Sex cord Stromal Tumors	Other
	→ Leydig Cell Tumor	→ Lymphoma
	→ Sertoli Cell Tumor	→ metastasis

Seminomatous GCT
→ Seminoma
→ Spermatocytic Seminoma

Non-Seminomatous GCT
t.me/latestpgnotes
→ Yolk sac tumor
→ Teratoma
→ Embryonal carcinoma
→ Choriocarcinoma

Risk factor and precursor lesion for testicular tumor   00:04:55

Risk factor

1. Testicular Dysgenesis syndrome
    → Cryptorchidism
    → Hypospadias
2. Klinefelter syndrome
3. Family History
4. Environmental toxins
5. i 12p, oct ³/₄ Nanog mutation

Precursor lesion

- ITGCN (Intra tubular Germ cell Neoplasm)
    ↓
Can give rise to all testicular tumors, Except :
→ Spermatocytic Seminoma
                → Teratoma

Active space

- Seminomatous GCT
  1. 2nd or 3rd decade
  2. Radiosensitive
  3. usually metastasize by lymphatics
  4. Better prognosis

Non- Seminomatous GCT
  1. No age Predilection
  2. Radioresistant
  3. Hematogenous
  4. poor Prognosis

Seminoma   00:10:07

1. Age: 20-30 years
   MC Testicular Tumours in adults
2. Radiosensitive
3. metastasizes by lymphatics → Paraaortic Lymph node enlargement
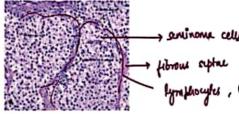4. Can Be associated with i 12 p
- clinically : Painless enlargement of testis
- Histopathology:

1. Nests of cells divided into poorly demarcated lobules
2. fibrous septae
3. Lymphoplasma in fibrous septae
4. cells are: round, Polygonal, with
   - distinct membrane
   - central nuclei
   - prominent nucleoli
   - perinuclear clearing →
   glycogen → PAS +

Lymphocyte, plasma cells, granulomas

Seminoma cells

gross → bulging, fleshy
No areas of Haemorr, necrosis

seminoma cells
fibrous septae
lymphocytes , '

- Immuno histochemical markers used :
1. PLAP+ (placental Alkaline Phosphatase +)
2. HCG +
3. LDH +
→ Never AFP +
- counter part of seminoma in an ovary → Dysgerminoma

Spermatocytic seminoma

- Elderly : Age → 60 Years
- ITGCN is not a Precursor Lesion
- Slow growing tumor
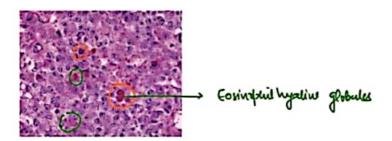- Excellent Prognosis

Yolk sac Tumors   00:20:09

- m.c. testicular tumor in infants and children
- AKA endodermal sinus tumor
- Age < 4 years
- Gross Presentation:
  → Area of hemorrhage, necrosis, cystic area
- H & E : → Network of cells In tubules, papillary, cord patterns.
  1. schiller duval bodies/ Glomeruloid bodies
  • Components: mesodermal core
  YOLK SAC TUM · Layer of Cells
  Parietal layer of cells

→ schiller duval
→ LUMEN

a. Eosinophil Hyaline globules t.me/latestpgnotes

→ Eosinophil hyaline globules

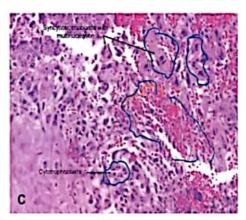- Immunohistochemical makers : AFP +
  α₁ Antitrypsin ⊕

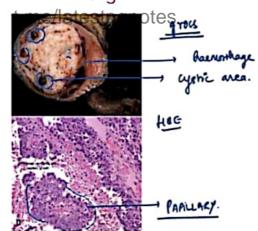## Choriocarcinoma and embryonal carcinoma   00:25:58

Choriocarcinoma

- Elderly
- No testicular enlargement
- Highly Aggressive chemo sensitive
- Usually metastasizes by hematogenous routes
- Produces : cannon ball mets (in lungs)
- Gross presentation: Hemorrhage and Necrosis
- H&E : - I. Cytotrophoblast

Active space

→ Polygonal cells with distinct borders.

a. **Syncytiotrophoblast**

→ Giant cells with multiple nuclei
(multinucleated)

– No villi formation

- marker : β HCG

C
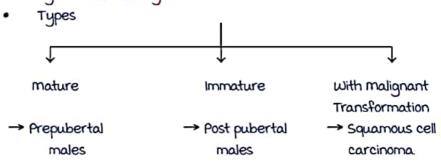
Embryonal Carcinoma

- age : 20-30 yrs
- grossly : Cystic, Mucinous areas
- H&E: → Primitive pleomorphic cells arranged in tubules, cord
- marker: CD 30+, Cytokeratin+

→ gross
→ haemorrhage
→ cystic area.

H&E

→ PAPILLARY.
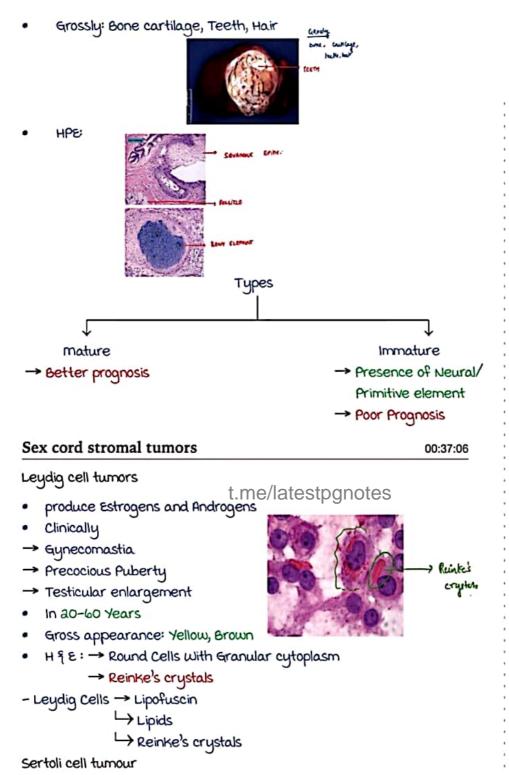
Teratoma   00:32:51

- Derivatives of $\geq$ 2 germ layers
- Cyst → dermoid cyst
- Types

mature	Immature	With malignant Transformation
→ Prepubertal males	→ Post pubertal males	→ Squamous cell carcinoma

- Grossly: Bone cartilage, Teeth, Hair

- HPE:

Types

Mature
→ Better prognosis

Immature
→ Presence of Neural/ Primitive element
→ Poor Prognosis

Sex cord stromal tumors   00:37:06

Leydig cell tumors

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- produce Estrogens and Androgens
- Clinically
→ Gynecomastia
→ Precocious Puberty
→ Testicular enlargement
- In 20-60 Years
- Gross appearance: Yellow, Brown
- H & E : → Round Cells with Granular cytoplasm
          → Reinke's crystals
- Leydig Cells → Lipofuscin
             ↳ Lipids
             ↳ Reinke's crystals

Reinke's crystals

Sertoli cell tumour

- Hormonally Silent Tumour
- Clinically Insignificant
- marker: Inhibin

Active space

Testicular lymphoma   00:41:12

- m.c Testicular Tumor In elderly (age > 60 years)
- usually bilateral
- usually DLBCL (diffused large b cell lymphoma)

Summary of testicular tumors

| Tumor	H&E	marker
1. Seminoma (m.c Testicular Tumor in Adults)	→ Seminoma cells → Fibrous septal infiltration by Lymphocytes	→ PLAP, LDH, HCG+ Oct 3/4, Nanog+
2. yolk Sac Tumor [m.c- children]	→ Schiller Duval body	→ AFP, α₁ Antitrypsin
3. Choriocarcinoma	→ Cytotrophoblast ↳ Syncytiotrophoblast no villi	→ HCG
4. Embryonal Carcinoma	→ Primitive cells	→ CD30+, CK+
5. Teratoma derived	→ All Germ Layers	→ -
6. Leydig cell tumor	→ Reinke's Crystal	→ -
7. Sertoli tumor	→ -	→ Inhibin
8. Lymphoma [m.c. Testicular tumor in elderly (>60yrs)]	→ Diffuse large B-cell lymphoma	→ BCL-6+, B-cell markers

Active space
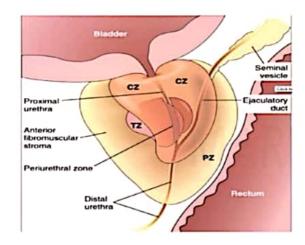
PROSTATE

- Average weight of prostate gland = 20 g
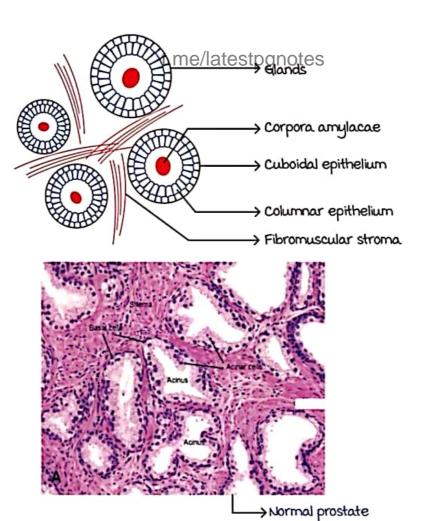
Anatomy and histology of prostate gland   00:01:10

Anatomy

Histology

→ Glands
→ Corpora amylacae
→ Cuboidal epithelium
→ Columnar epithelium
→ Fibromuscular stroma

→ Normal prostate

• Breast biopsy stroma is fatty (to differentiate it from prostate biopsy)

Benign prostatic hyperplasia
00:06:31

• Now Known as : Nodular Hyperplasia of Prostate

• m.c prostatic disease

• Clinically : usually affects Transitional zone

↓

→ Difficulty in micturition

→ Dysuria

→ Nocturia

• Pathogenesis :   Testosterone

5 α reductase -2 ↓

Dihydrotestosterone on stromal cells

↓

acts on androgen receptors

on stromal and epithelial cells

↓

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Nodular Hyperplasia
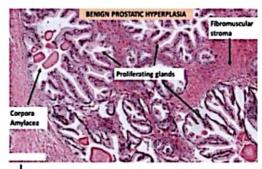
Proliferation of both stromal and epithelial cells

Warning : Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with marrow Edition 4 videos.

• Gross pathology : large, white nodules.

FIGURE 45.3   Gross photograph of benign prostatic hyperplasia

BENIGN PROSTATIC HYPERPLASIA
Fibromuscular stroma
Proliferating glands
Corpora Amylacea

↳ Weight of prostate ↑ to
60 - 100 g

↳ H & E : Proliferation of :
→ Glands
→ Stroma

Prostate adenocarcinoma

00:12:58

- Risk factors :
  1. Age > 50 years
  2. Black population > white population
  3. High fat diet

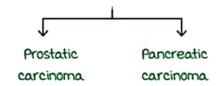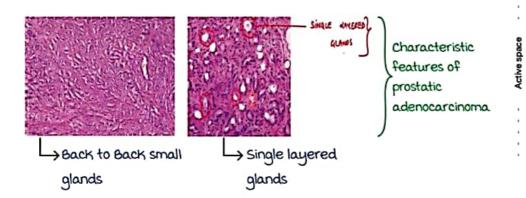- Foods that show protective function against prostate cancer :
  1. Lycopenes
  2. Vitamin D
  3. Selenium
  4. Soy

- Genetic factors :
  1. BRCA2 gene mutations
  2. ↓ Expression E-Cadherin
  3. Hypermethylation of Glutathione S Transferase.
  4. Chromosomal rearrangement which juxtaposes ETS Fusion gene with TMPRSS2 gene (Androgen Receptor Regulator)

- Precursor lesion : PIN (Prostatic Intraepithelial Neoplasia)
  → within glands, do not invade stroma
  → intact basement membrane

- Gross pathology : Grey white tumor, affects peripheral zone.

- H & E:
  1. Smaller glands, back to back
  2. Loss of myoepithelial layer, single layered glands
  3. Perineural invasion.

| Prostatic carcinoma | Pancreatic carcinoma |

→ Back to Back small glands

→ Single layered glands

SINGLE LAYERED GLANDS

Characteristic features of prostatic adenocarcinoma
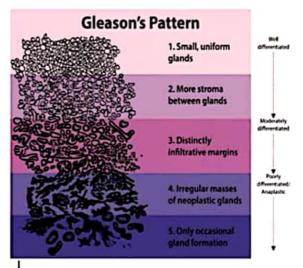
Active space

Prostatic adenocarcinoma : Gleason's score and markers   00:21:56

Gleason's score

- Histopathological score
- 5 grades depending on architectural / glandular pattern.

Gleason's Pattern

1. Small, uniform glands — Well differentiated
2. More stroma between glands
3. Distinctly infiltrative margins — Moderately differentiated
4. Irregular masses of neoplastic glands — Poorly differentiated / Anaplastic
5. Only occasional gland formation

↳ Gleason's pattern and respective grades

- Gleason's score = Primary grade   +   secondary grade.
  (1ˢᵗ dominant pattern)   (2ⁿᵈ most dominant pattern)
- A gleason's score of 3+4 has better prognosis than 4+3 (Dominant pattern with lower score)

markers

- Immunohistochemical markers : ⟶ AMACR (α – methyl Acyl Coenzyme A Racemase)
  ↳ PCA 3

- Tumour markers : 1. PSA (Prostate Specific Antigen)

Age :	Normal PSA
40 – 49 years	2.5 ng / ml
50 – 59 years	3.5 ng / ml
60 – 69 years	4.5 ng / ml
70 – 79 years	6.5 ng / ml

  2. PSA density $= \dfrac{\text{serum PSA}}{\text{volume of gland (USG)}}$

  3. PSA velocity
     → 3 samples taken over 2 consecutive years
     → > 0.75 ng / ml / year rise : patient can develop malignancy

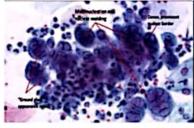 4. Free PSA / Bound PSA
     → Bound PSA have a lesser value

Active space

FEMALE GENITAL TRACT: CERVIX

Infections of female genital tract
00:01:44

I. Herpes Simplex virus

HSV – 1: oropharyngeal
HSV – 2: genital

↑
HSV–2

Features:
multinucleation, nuclear molding
Ground glass appearance of nuclei
↳ Also seen in : Hepatitis B infection

2. Molluscum contagiosum
Pox virus 1 (most prevalent), 2, 3, 4
Pearly, dimpled dome shaped lesions.

HPE :
Pinkish, intracytoplasmic inclusions in
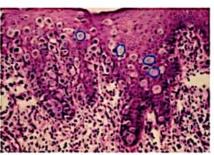the epidermis : molluscum bodies

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3. Trichomonas vaginalis – ovoid,
flagellated organism
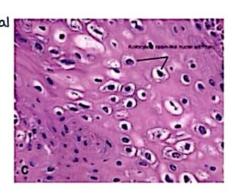strawberry cervix

4. Gardnerella vaginalis – gram negative organism fishy smelling
discharge clue cell ⊕

Active space

Vulval lesions

00:06:23

1. Paget's disease of vulva
   Paget's cell : large cell with perinuclear halo indicates
   carcinoma in-situ

2. Condyloma acuminatum – genital
   warts HPV 6, 11 (low risk HPV)
   warty verrucous lesions
   HPE:
   Koilocytic atypia ⊕
   Koilocytes :
   Large cells, thick
   membrane, resin like nucleus,
   perinuclear halo.

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Vaginal lesions

00:09:48

Normal lining : non – keratinized stratified squamous epithelium

Lesions

Squamous cell carcinoma	Embryonal rhabdomyosarcoma	Clear cell adeno Ca.
• upper posterior vagina.	• a/k/a Sarcoma botryoides	Risk factor: Diethyl stilbesterol (DES)
• HPV, multiple sexual partners	• large polypoid mass, grape like clusters	
• HPE: Keratin pearls Desmosomes.	• affect infants & children	
• Marker: cytokeratin	• HPE: Tennis racquet cells Small cells, eccentric nuclei, cytoplasmic protrusions	
	• IHC: Desmin, myogenin, myoD1	
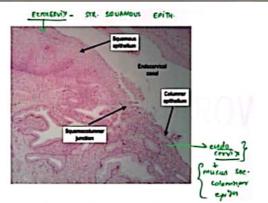
Active space

Lesions of cervix

00:14:41
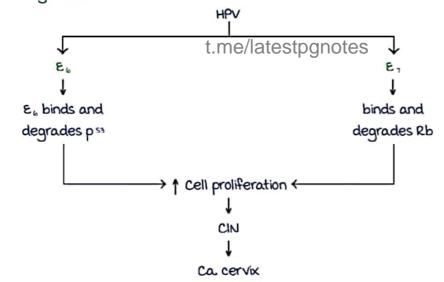
- Ectocervix: stratified squamous epithelium
- Endocervix " mucus secreting columnar epithelium.
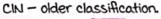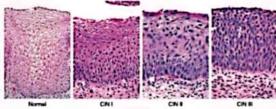
Pathogenesis of CIN (cervical intraepithelial neoplasia) and Ca Cervix

HPV infection.

High risk strains	Low risk strains
HPV 16, 18	HPV 6, 11
• CIN	Cause genital warts –
• Ca cervix	condyloma acuminatum

Pathogenesis

HPV

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E_6	E_7
E_6 binds and degrades p^{53}	binds and degrades Rb

→ ↑ Cell proliferation ←
↓
CIN
↓
Ca. cervix

CIN — older classification.

CIN I : Atypical cells in lower 1/3rd of epithelium

CIN II : Atypia in lower 2/3rd.
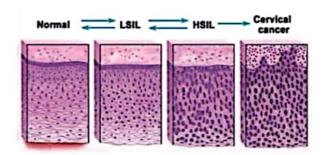
CIN III : entire thickness → atypical cells.

CIN : Atypia limited by basement membrane

Active space

New classification — SIL (Squamous intraepithelial lesion)

LSIL : Low grade SIL (lower 1/3rd involved)
HSIL : High grade SIL (involves entire epithelium)

Cervical Changes

Normal ⇄ LSIL ⇄ HSIL → Cervical cancer

Histopathological criteria for diagnosis:
  Pleomorphism
  Nuclear enlargement
  Hyperchromasia   } Nuclear atypia.
  Prominent nucleoli

         +
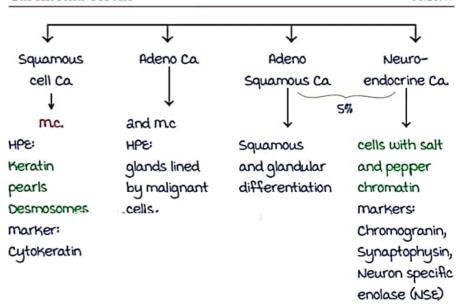
  Koilocytic atypia.

marker of viral load / K; 67
              P — 16

Carcinoma cervix   00:23:47

Squamous cell Ca	Adeno Ca	Adeno Squamous Ca	Neuro-endocrine Ca.
↓ m.c.	2nd m.c	5%	
HPE: Keratin pearls Desmosomes marker: Cytokeratin	HPE: glands lined by malignant cells.	Squamous and glandular differentiation	cells with salt and pepper chromatin markers: Chromogranin, Synaptophysin, Neuron specific enolase (NSE)
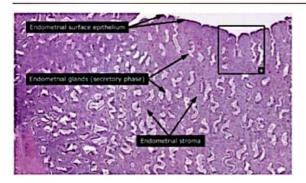
Papanicolaou stain (PAP stain) → cervical smear examination
Vaccines against HPV → Cervarix, Gardasil.

Active space
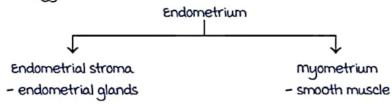
UTERUS AND ENDOMETRIUM

Endometrium   00:00:23

- Histology :

```
                    Endometrium
          ┌─────────────┴─────────────┐
          ↓                           ↓
  Endometrial stroma             myometrium
  - endometrial glands           - smooth muscle
```

- Endometriosis
  - Presence of endometrial glands and stroma outside the uterus
  - most common site : Ovaries
          other sites : Uterine ligaments
                         Pelvic peritoneum
                         Rectovaginal septum
  - Theory : Retrograde menstruation
  - Chocolate cyst of ovary
                    when lesions bleed
                                    ↓
                        ↓ blood → brown
              Convert ovaries to cystic structures
                         │
                         ↓
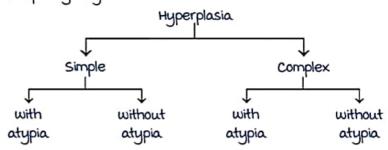
                Chocolate cysts of ovaries
  - Endometriosis increases the risk of :
    • Endometrioid cancer
    • Clear cell cancer of ovary

- Adenomyosis
  - Presence of endometrial glands in the myometrium
  - 2 - 3mm away from endomyometrial junction.

- Endometrial hyperplasia
  - Increased proliferation of endometrial glands relative to stroma.
    Risk factor : prolonged estrogen stimulation
  - Gene : PTEN gene mutation of chromosome 10

    ↓

    increased risk of endometrial hyperplasia and carcinoma.
  - morphologically :

```
                        Hyperplasia
                ┌───────────┴───────────┐
              Simple                  Complex
          ┌─────┴─────┐          ┌─────┴─────┐
        with       without     with       without
       atypia      atypia     atypia      atypia
```

Endometrial carcinoma   00:08:30
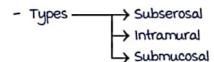
|	Type I	Type II
Age	55-65y	60-75y
Risk factors	obesity, DM, HTN unopposed estrogen endometrial hyperplasia	thin physique endometrial atrophy
Genetics	PTEN, PI3K KRAS, ARID-1a MSI	P53 mutations, aneuploidy
morphologic type	Endometrioid	clear cell serous mixed mullerian
Prognosis	Indolent, lymphatics	aggressive, intraperitoneal spread
Development schematics	Proliferative endometrium ↓ PTEN simple hyperplasia ↓ hMLH1 Complex hyperplasia ↓ KRAS Complex atypical hyperplasia ↓ β-catenin ↓ PIK3CA Endometrial carcinoma Type I	Atrophic endometrium ↓ p53 ↓ Aneuploidy Endometrial intra-epithelial carcinoma ↓ Serous carcinoma Type II

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Active space

Myometrium

00:14:18

- Lesions of myometrium : Leiomyoma
  Leiomyosarcoma

- Leiomyoma:
  - Fibroid tumor
  - most common tumor in females
  - Benign tumor from a smooth muscle
  - Genetics :
    - → t (12:14)
    - → MED 12 gene mutation
    - → partial deletion of 7q

  Gross pathology : well circumscribed, grey-white
    cut surface — whorled appearance

  - Types
    - → Subserosal
    - → Intramural
    - → Submucosal
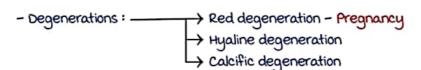
  microscopy :
  - Intersecting fascicles of
    smooth muscle cells
  - No atypia
    no mitosis
    no pleomorphism

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  - If atypia +
    giant cells   ⟶   Symplastic
                          Leiomyoma

  - Degenerations :
    - → Red degeneration – Pregnancy
    - → Hyaline degeneration
    - → Calcific degeneration

  - marker : SMA (smooth muscle actin)

- Leiomyosarcoma : malignant tumor of uterine smooth muscles
  - Criteria : > 10 mitosis / 10 HPF,
      more atypia, more necrosis

Active space
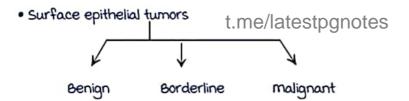
OVARIAN TUMORS

Classification   00:00:13

```
                    Ovarian tumors
         ┌──────────┬──────────┬──────────┐
         ↓          ↓          ↓          ↓
    Surface      Germ cell   Sex cord    metastasis
   epithelial    tumors      stromal tumors
```

• Serous   • Dysgerminoma   • Fibroma   • Krukenberg
                                                            tumor
• mucinous   • Yolk sac tumor   • fibrothecoma

• Clear cell   • choriocarcinoma

• Endometrioid   • Teratoma   • Granulosa cell
                                        tumor

• Transitional/   • Embryonal   • Leydig cell
  Brenner   carcinoma   tumor
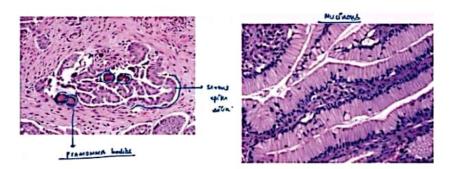
Surface epithelial tumors   00:03:20

• Surface epithelial tumors

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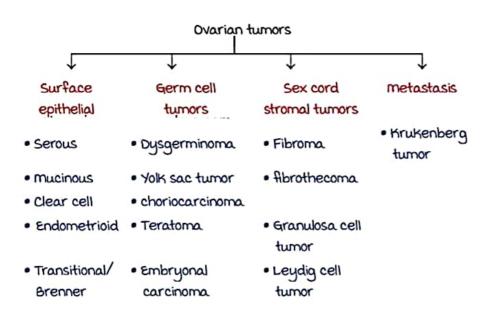
```
         ┌──────────┬──────────┐
         ↓          ↓          ↓
      Benign    Borderline   Malignant
```

• Derived from surface coelomic epithelium

• most common ovarian tumors

Serous epithelial tumor	mucinous epithelial tumor
• 60% benign	• 80% benign
• Bilateral	• Unilateral
• Genetics – BRCA1, BRCA2, p53	• genetics – K-RAS mutations
• Risk factors – multiparity, family history	• risk factor – smoking
• Gross – uniloculated, clear fluid	• multiloculated, thick fluid
• microscopy – serous ciliated epithelial cells	• microscopy – Tall columnar non-ciliated cells with apical mucin.
• Psamomma bodies +	• psamomma bodies –

Active space

Mucinous

★ Psamomma bodies are also seen in:-
1. Papillary carcinoma of thyroid
2. Papillary renal cell carcinoma
3. Serous Cystadenocarcinoma of ovary
4. Meningioma
5. Prolactinoma

★ Tall columnar cells with apical mucin

★ Pseudomyxoma peritonei (Implants of mucinous carcinoma in the peritoneum)
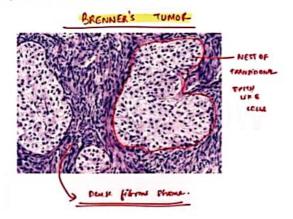
★ Clear cell tumors:-
- Composed of cells with clearing, due to glycogen
$$\downarrow$$
PAS +
- Can be associated with ⎡→ Endometriosis
⎣→ Diethylstilbestrol (DES)

★ Endometrioid carcinoma
- Resembles benign or malignant endometrial glands
- Can be associated with endometriosis

★ Brenner tumor A/K/A transitional cell tumors
- Unilateral solid benign tumors
- microscopy: nests of cells that resembles the transitional epithelium of urinary bladder, dense fibrous stroma & coffee bean nuclei – nuclear grooves

Active space
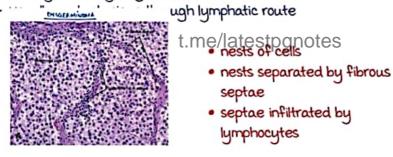
Coffee bean nuclei or nuclear grooves are also seen in:-
Papillary carcinoma of thyroid
Langerhans cell histiocytosis
Brenner tumor
Granulosa cell tumor

BRENNER'S TUMOR
— NEST OF TRANSITIONAL EPITHELIUM LIKE CELL
Dense fibrous stroma.
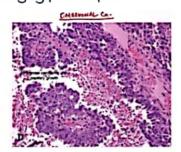
Germ cell tumors of the ovary   00:14:16
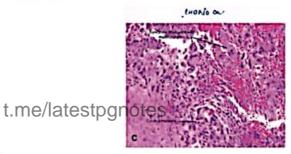
- Dysgerminoma
  - Counterpart of seminomas in males
  - Highly radiosensitive
  - Usually seen in young women
  - .... ugh lymphatic route

DYSGERMINOMA

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  - nests of cells
  - nests separated by fibrous septae
  - septae infiltrated by lymphocytes

  - Tumor markers are
    - PLAP +
    - OCT 4 +
    - Nanog +

- Embryonal carcinoma
  - Arrangement of cells are in cords, sheets or papillary
  - Highly pleomorphic

EMBRYONAL Ca.

Active space
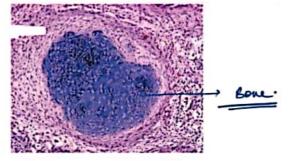
- **Yolk sac tumor / Endodermal sinus tumor**
  - Centrally, there is a blood vessel surrounded by tumor cells and mimic glomerulus glomeruloid bodies, also seen in glioblastoma multiforme.
  - Presence of hyaline globules
  - Commonly seen in children
  - AFP +
    α-1 antitrypsin +

- **Choriocarcinoma**
  - Usually occurs in women >60 years
  - Extreme hemorrhage & necrosis is seen
  - Two kinds of cells   →   cytotrophoblast
    syncytiotrophoblast with multinucleation
  - Usually metastasize to lungs – Cannonball metastasis
  - HCG +ve

- **Teratoma**
  - Presence of elements from multiple germ layers like hair, bone, cartilage etc

Teratoma		
mature	Immature	monodermal
- Benign	- malignant	- Struma ovarii (presence of thyroid tissue in ovary)
- No primitive elements	- Presence of primitive / neural elements	
- If cystic, dermoid cyst	- Poor prognosis	
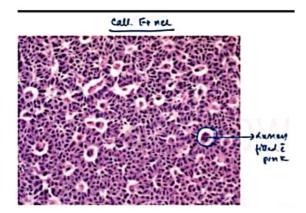
Sex cord stromal tumors   00:22:25

- Elaborate estrogen or progesterone
- Can present as precocious puberty

- Fibroma
→ Histologically composed of well differentiated fibroblasts.
→ Benign, unilateral, solid
→ Associated with meigs Syndrome ⟶ Fibroma
                                           Ascites
                                           Right hydrothorax

- Thecoma
→ Composed of spindle shaped cells with lipid droplets
   (vacuolated cytoplasm)
   Oil red O stain- positive
→ Benign, unilateral, solid
- Fibrothecoma – histologically contains features of both fibroma
                  and thecoma
- Granulosa cell tumor
- 5% of ovarian tumors
- Elaborate estrogen and can cause precocious puberty
                                  Endometrial hyperplasia
                                  Endometrial carcinoma
- Genetic – FOXL2 gene
- marker – inhibin
- Gross – yellowish in colour due to lipids
   microscopy – cells arranged in cords and sheets
              - Call-Exner bodies
              - Coffee bean nuclei

Call. Exner

→ lumen
filled with
pink

Active space
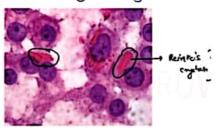
- Hilus cell / Leydig cell tumor
  - Elaborates testosterone
  - Reinke's crystals also seen in normal Leydig cells but its number is significantly increased in tumors
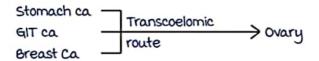
Reinke's crystals

Metastasis

00:29:52

Stomach ca
GIT ca
Breast Ca
} Transcoelomic route → Ovary
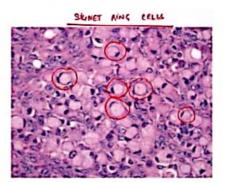
- Krukenberg's tumor
  → Stomach Carcinoma going to the ovary through transcoelomic spread
  → Bilateral, Symmetrically enlarged ovaries with intact capsule
  → microscopy: Signet ring cells — has intracellular mucin

SIGNET RING CELLS

Gestational trophoblastic diseases

00:32:41

1. Hydatidiform mole
2. Invasive mole [when hydatidiform mole goes to lungs or any other site]
3. Choriocarcinoma
4. Placental site trophoblastic tumor [PSTT]

★ Hydatidiform mole

Partial mole	Complete mole
• Single egg fertilized by 2 sperms	• One empty egg fertilized by 1 sperm that duplicates
$\underset{\sim o23}{\overset{\sim o23}{}} + \textcircled{23} \rightarrow 69\ chromosomes$	$\underset{duplicates}{\overset{\sim o23}{}} + \bigcirc \rightarrow 46\ ch$
Triploid	Diploid
• villous edema is present some villi are normal	• All villi are edematous
• Fetal parts +	• Fetal parts −
• Focal trophoblastic proliferation	• Diffuse trophoblastic proliferation
• minimal risk for choriocarcinoma	• 2-3% chance of developing choriocarcinoma

→ Gross : grape like clusters: thin, translucent & cystic ,also seen in sarcoma botryoides.

Active space

THYROID / NON-NEOPLASTIC TUMORS

Thyroid gland   00:00:57

→ 'H' shaped or Butterfly shaped gland
→ Both lobes are divided by isthmus
→ Weight – 15-25 grams
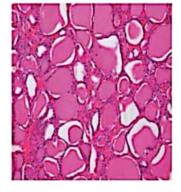
Histology:

→ Follicles lined by low cuboidal epithelium
→ Center of follicles
        ↓
    Colloid (pink)
        ↓
'Thyroglobulin' – PAS+
→ Parafollicular / 'C' cells of thyroid
    - Produces 'Calcitonin'
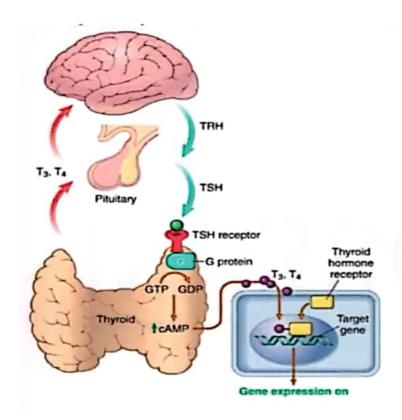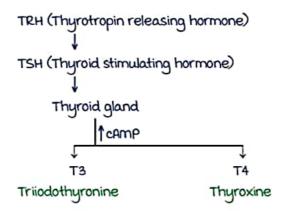
Hypothalamus–pituitary–thyroid axis   00:03:20

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Active space

TRH (Thyrotropin releasing hormone)
↓
TSH (Thyroid stimulating hormone)
↓
Thyroid gland
|↑cAMP

T3   T4
Triiodothyronine   Thyroxine
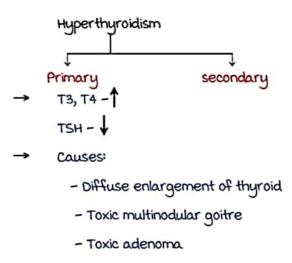
Hypothyroidism and hyperthyroidism

Clinical presentation:

Hypothyroidism	Hyperthyroidism
• Hair loss	• Hair loss
• Inability to think clearly	• Bulging eyes
• Goiter (enlarged thyroid)	• Goiter (enlarged thyroid)
• Reduced heart rate	• Heart palpitations
• Strong fatigue	• Tremors
• Sensitivity to cold	• Heat intolerance
• Dry skin	• Sleep disturbances
• Weight gain	• Weight loss
• Puffiness	• Shortness of breath
• Memory problems	• Diarrhoea
• Constipation	• Increased appetite
• Irregular menstrual periods	• Irregular menstrual periods
• Severe PMS	• Muscle weakness
• Depression, mood swings	• Sweating
• Joint, muscle pain	• Anxiety, nervousness
• High cholesterol	• Depression, mood swings

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Hyperthyroidism

Primary   secondary
→   T3, T4 – ↑

     TSH – ↓

→   Causes:

        – Diffuse enlargement of thyroid

        – Toxic multinodular goitre

        – Toxic adenoma

Active space

Grave's disease   00:07:25

→ MC cause of endogenous hyperthyroidism

→ F > M, 20 – 40 yrs

→ Type II hypersensitivity reaction

   - Antibody mediated

      1) Antithyroid stimulating Immunoglobulin

      2) LATS (long-acting thyroid stimulator)

→ Autoimmune etiology: associated with CTLA4, PTPN 22, HLA DR3, HLA B8.

→ Clinical triad:

   • Hyperthyroidism

   • Infiltrative opthalmopathy (exopthalmos)

   • Infiltrative dermopathy (pretibial myxedema)

→ morphology:

   • Gross : meaty/Beefy red.

   HPE : 1) Hyperplastic follicles

      2) Formation of papillae (absence of core)

      3) Scalloping of colloid

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Symmetrically enlarged   H & E
meaty appearance

A

microscopic appearance

→ whitish area along the cuboidal epithelium where colloid takes the
   shape of epithelium – 'Scalloping of colloid'

Active space
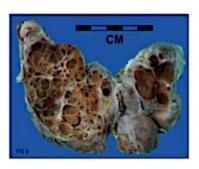
Multinodular goitre
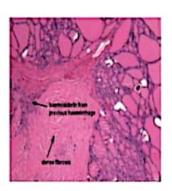
00:13:27

Gross morphology : multiple nodules filled with colloid

HPE:

→ Follicles of various sizes

→ Filled with colloid

→ Degenerative changes

    1) Calcification

    2) Hemosiderin laden macrophages

    3) Cystic changes

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Hypothyroidism

Types ⟶ Primary
      ⟶ Secondary

→ mc cause of hypothyroidism − Iodine deficiency

→ mc cause of hypothyroidism in Iodine sufficient areas of world ⎱ Hashimoto's Thyroiditis

Hashimoto's thyroiditis:

→ Pathogenesis:

  − Autoimmune etiology

  − Genetic − CTLA 4, PTPN 22.

  − Antibody mediated

    • Anti TPO Ab

    • Anti microsomal Ab

    • Anti thyroglobulin Ab

Active space

→ Grossly: Diffuse enlargement of thyroid gland

HPE:
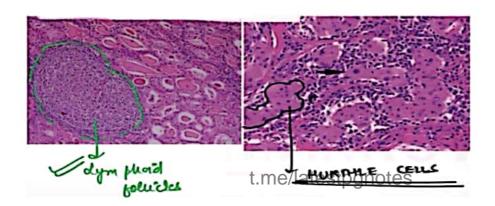
1) Lymphoid follicles with germinal centers

↓

Struma lymphomatosum

2) Hurthle cell / oncocytic change

- Cells with abundant granular, eosinophilic cytoplasm

↓

Excess of mitochondria

— lymphoid follicles

HURTHLE CELLS

→↑ Risk for developing — papillary carcinoma thyroid

→↑ Risk of developing — Extranodal marginal B cell Lymphoma

Clinically:

Initially → hashitoxicosis

↓

hypothyroidism

Subacute lymphocytic thyroiditis   00:22:47

→ Occurs in pregnancy

→ Self limiting condition

HPE: - predominance of lymphocytes

- Absence of Hurthle cell change

De Quervain's thyroiditis/Granulomatous Thyroiditis

→ Painful thyroid gland

→ Occurs following viral infection (measles, mumps)

→ Self limiting condition

HPE : granulomas & lymphocytes

Reidel's Thyroiditis:
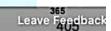
→ Stony hard thyroid gland

$\downarrow$

Due to fibrosis
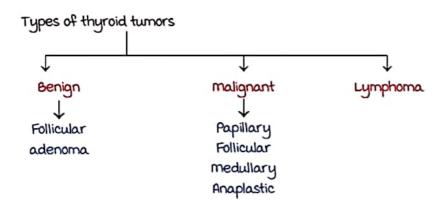
→ D/D for thyroid malignancy

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Active space

THYROID TUMORS

Types of thyroid tumors

| Benign | Malignant | Lymphoma |

Benign → Follicular adenoma

Malignant → Papillary
Follicular
Medullary
Anaplastic
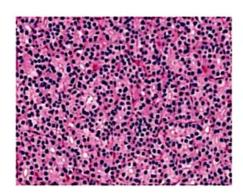
Criteria to predict malignancy in a thyroid nodule

1) Solitary
2) Solid
3) young male
4) Cold nodule
5) Previous history of radiation exposure

Follicular adenoma

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on histopathological examination – Large number of follicles with
(H&E)   scanty colloid

Active space

Malignant thyroid tumors   00:03:44

Papillary	Follicular	medullary	Anaplastic
1) m.c. 2) Best prognosis 3) Arises from follicular cells	follicular cells	Para follicular cells/ C cells of thyroid	Least common worst prognosis Follicular cells
4) Risk factors – • Radiation exposure • Thyroglossal cyst • Hashimoto's thyroiditis	• Iodine deficiency • multinodular goiter		
5) metastasis: Lymphatic	Hematogenous	Both	Both
6) Genetics • BRAF – m.c RET – PTC	K- RAS PI3K	Ret gene on chromosome 10	P53

Ret gene on chromosome 10

Sporadic   Familial
↓   ↓
• Unilateral   • Bilateral
• Adults   • multi centric
• Poor   • MEN 2
Prognosis   Syndrome

Malignant tumor - papillary carcinoma   00:09:20

1)   Papillae with fibrovascular core
2)   Lined by cells → Orphan Annie eye nuclei
                         ↓
            optically clear nuclei
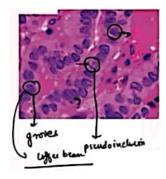
3)   Nuclear pseudoinclusions
4)   Nuclear grooves - coffee bean nuclei

5) Psamomma bodies

Papillae with fibrovascular core

groves
coffee bean pseudoinclusion

pseudoinclusion bodies
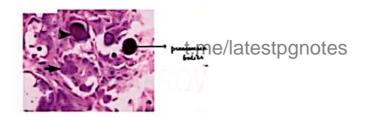
Tumors that show nuclear groove
Papillary carcinoma of thyroid
Granulosa cell tumor
Brenner's tumor
Langerhan cell histiocytosis

Variants - papillary carcinoma of thyroid   00:14:55

1) Follicular variant - Cells arranged in follicles
                        ↓
            but nuclear features are those of
                    Papillary carcinoma

2) Tall cell variant
3) Columnar cell variant
4) Papillary microcarcinoma - < 1cm
5) Dense sclerosing variant

Active space
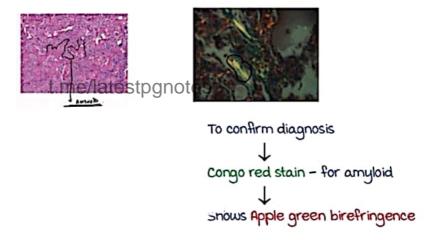
Malignant tumor - follicular carcinoma   00:16:30

- on H § E - Cells arranged in follicles, Capsular/ vascular invasion
    - useful for differentiation of follicular adenoma and follicular carcinoma

- FNAC is not useful for diagnosis of follicular carcinoma
    ↓
  because on FNAC - Capsule/blood vessel Sample is not taken

- H § E - is the gold standard for diagnosis

Malignant tumor - medullary carcinoma   00:19:33

- H § E - Spindle cells
    Amyloid → A cal amyloid (cal - Calcitonin)
- Tumor marker - Calcitonin
- CEA (carcinoembryonic antigen) - a useful marker for calcitonin negative medullary carcinoma.

To confirm diagnosis
    ↓
Congo red stain - for amyloid
    ↓
shows Apple green birefringence
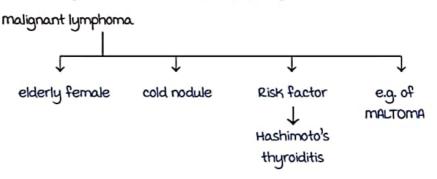
Malignant tumor - anaplastic carcinoma, lymphoma   00:22:16
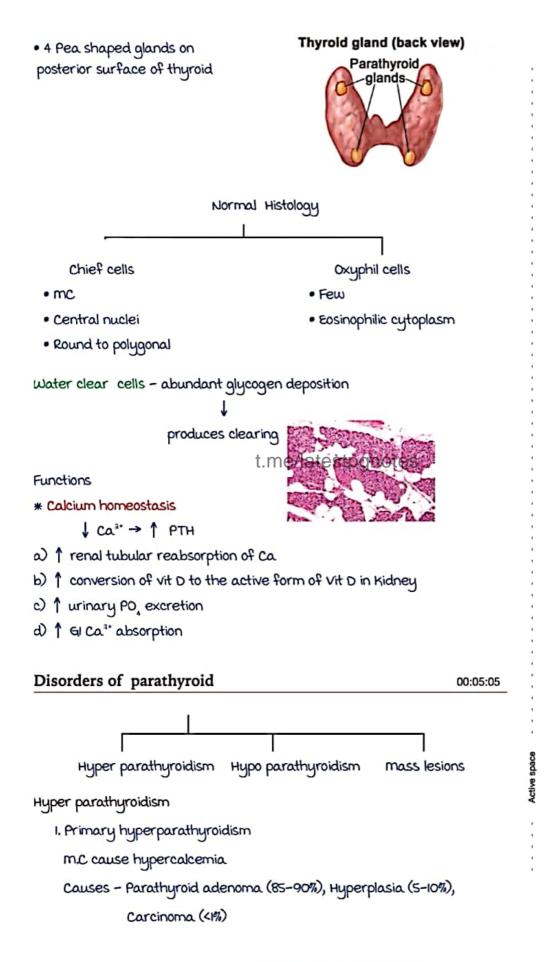
- H § E - spindle cells
    Sarcomatoid cells } Pleomorphic cells
    giant cells
- Usually arises in the setting of papillary carcinoma

malignant lymphoma
|
elderly female   cold nodule   Risk factor   e.g. of MALTOMA
                                    ↓
                                Hashimoto's
                                thyroiditis

Active space

PARATHYROID

• 4 Pea shaped glands on posterior surface of thyroid

Thyroid gland (back view)

Parathyroid glands

Normal Histology

Chief cells	Oxyphil cells
• mc	• Few
• Central nuclei	• Eosinophilic cytoplasm
• Round to polygonal	

Water clear cells – abundant glycogen deposition

↓

produces clearing

Functions

* Calcium homeostasis

$$\downarrow Ca^{2+} \rightarrow \uparrow PTH$$

a) ↑ renal tubular reabsorption of Ca

b) ↑ conversion of vit D to the active form of Vit D in Kidney

c) ↑ urinary PO_4 excretion

d) ↑ GI Ca^{2+} absorption

Disorders of parathyroid   00:05:05

Hyper parathyroidism	Hypo parathyroidism	mass lesions

Hyper parathyroidism

   1. Primary hyperparathyroidism

   mc cause hypercalcemia

   Causes – Parathyroid adenoma (85-90%), Hyperplasia (5-10%),

      Carcinoma (<1%)

Active space

Pathology   1. cyclin D₁ gen inversion

$$\downarrow$$

↑ Expression of cyclin D₁ (regulation of cell cycle)

$$\downarrow$$

↑ Cellular proliferation

$$\downarrow$$

Adenoma

2. mutation in MEN I gene

$$\downarrow$$

↑ Expression of menin

morphology

1. Adenoma - solitary lesion involves single gland

– Encapsulated

HPE of parathyroid adenoma   00:10:36

Sheets / cords of chief cells

$$\downarrow$$

Central nuclei
round to polygonal

Sometimes ↑ oxyphil cells

$$\downarrow$$
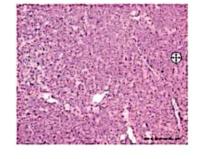
oxyphil adenoma / Hurthle cell adenoma

Parathyroid hyperplasia

• Involves all 4 parathyroid glands

$$\downarrow$$

microscopically same as adenoma

sometimes ↑ water clear cells

Active space
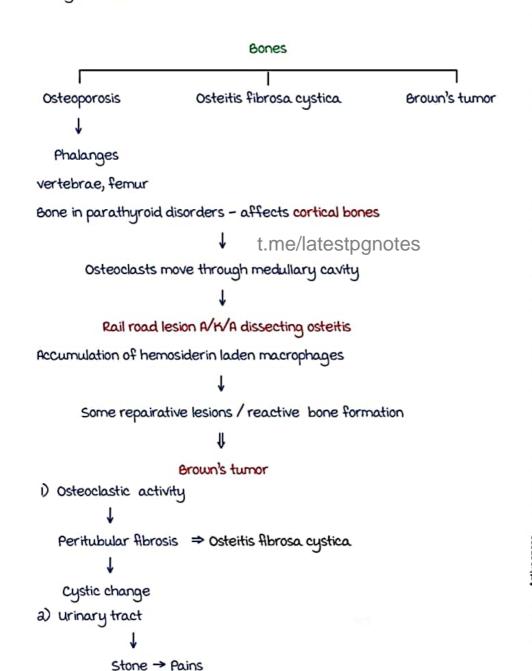
Parathyroid carcinoma

- Rare

- Criteria for diagnosis – metastasis (most endocrine)

Clinical features of hyperparathyroid   00:17:00

- Painful bones

- Renal stones

- Abdominal groans

- Psychic moans

Bones

Osteoporosis   Osteitis fibrosa cystica   Brown's tumor

↓

Phalanges

vertebrae, femur

Bone in parathyroid disorders – affects cortical bones

↓   t.me/latestpgnotes

Osteoclasts move through medullary cavity

↓

Rail road lesion A/K/A dissecting osteitis

Accumulation of hemosiderin laden macrophages

↓

Some repairative lesions / reactive bone formation

⇓

Brown's tumor

1) Osteoclastic activity

↓

Peritubular fibrosis ⇒ Osteitis fibrosa cystica

↓

Cystic change

2) urinary tract

↓

Stone → Pains

3) Neuromuscular / neurological abnormality

Active space

Secondary hyperparathyroidism
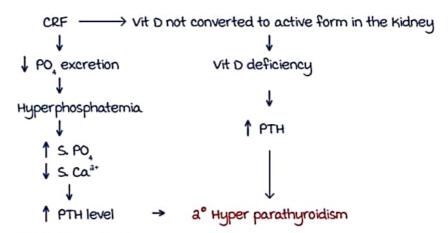
Cause – chronic renal failure (mcc)

Due to prolonged hypocalcemia

Other causes
1. Vit. D deficiency
a. malabsorption

CRF   ⟶   Vit D not converted to active form in the Kidney
  ↓   ↓

↓ PO_4 excretion   Vit D deficiency
     ↓
Hyperphosphatemia
     ↓   ↑ PTH
  ↑ S. PO_4
  ↓ S. Ca^{2+}
     ↓
  ↑ PTH level   →   2° Hyper parathyroidism

Reversible disease
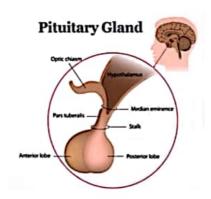
Tertiary hyperparathyroidism

     Parathyroid gland
          ↓

  Starts producing PTH even with hypocalcemia treatment

    autonomously
        ↓

    ↑ PTH

Active space

PITUITARY GLAND
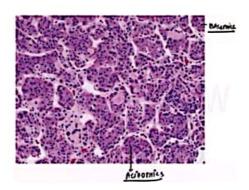
Pituitary Gland

Anterior pituitary [80%]	ACTH GH MSH TSH Gonadotropins (LH & FSH) Prolactin	Adrenal cortex Bone and muscle Skin Thyroid Testis and Ovaries Breast
Posterior pituitary [20%]	Oxytocin, ADH (vasopressin)	Breast, Kidney

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microscopy:

Acidophils
- Somatotrophs
- Lactotrophs

Basophils
- Corticotrophs
- Basophilic cells
- Thyrotrophs
- Gonadotrophs

- Pituitary adenoma
- most common pituitary tumor
- most common type: prolactinoma
  (amenorrhoea + galactorrhoea)

Active space

- Classifications of pituitary adenomas

I — 1 : Corticotrophic — Cushing's and Nelson's syndrome
2 : Somatotrophic — Acromegaly, gigantism
3 : Lactotrophic — Prolactinoma
4 : Mammosomatotrophic — Acromegaly, gigantism, hyperprolactinemia
5 : Thyrotrophic — Hypothyroidism and hyperthyroidism
6 : Gonadotrophic — Hypogonadism, mass effect

II Pituitary Adenoma → Microadenoma   <1 cm
                       → Macroadenoma   >1 cm

III Pituitary adenoma → Functional
                       → Non - functional

- microscopic features of pituitary adenomas
- Round to polygonal monomorphic cells
- Sparse supportive connective tissue
- Cellular monomorphism
- Absence of significant reticulin network

- Gross : soft, well circumscribed
- Pituitary carcinoma — only criteria to distinguish is metastasis

Craniopharyngioma   00:07:08

- Arises from Rathke's pouch
- 3-4 cm encapsulated tumor
- Can produce pressure effects on optic chiasma
- Gross - cyst with yellow / brown oil
                    ↓
              machine oil
- microscopy:

	Adamantinomatous	Papillary
Age group	Children	Adults
Stratified squamous epithelium	⊕	⊖
Wet keratin	⊕	⊖
Calcification	⊕	⊖
Cysts	⊕	⊖
Reticulin	⊕	⊖

Active space

TUMORS OF ADRENAL MEDULLA

Pheochromocytoma

Rule of 10's – 10% of Pheochromocytoma are bilateral

10% occur in children

10% are malignant – criteria (metastasis)

10% extra adrenal

10% do not present with hypertension

MEN – 2A – chromosome 10
MEN – 2B – chromosome 10
Neurofibromatosis type I (NF-I) – chromosome 17
VonHippel-lindau (VHL) – chromosome 3

C/F – Pressure (episodic)
Pain (episodic headache)
Pallor
Perspiration
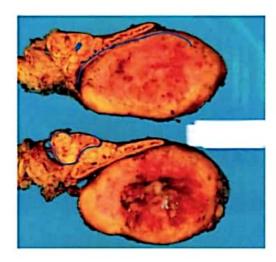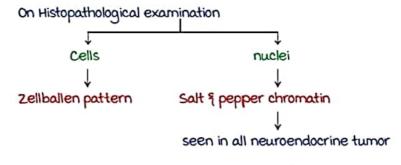
Gross findings – Tan yellow adrenal gland
↓
Due to chromaffin reaction
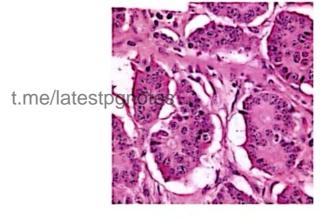
On Histopathological examination

```
                    ┌──────────────┴──────────────┐
                    ↓                              ↓
                  Cells                          nuclei
                    ↓                              ↓
          Zellballen pattern           Salt & pepper chromatin
                                                   ↓
                                     seen in all neuroendocrine tumor
```


Salt and pepper
chromatin

Immunohistochemical markers (IHC) — NSE (Neuron specific
                                          enolase)
                                      - Chromogranin
                                      - Synaptophysin

Sustentacular cells   – in between the nests of Zellballen

                      - S-100 Positive

• Salt & pepper chromatin } → found in other neuroendocrine
IHC markers   }   tumors
                                               ↓
                                         Carcinoid tumors
                                         Paragangliomas
                                         carotid body tumors
                                         small cell lung cancer
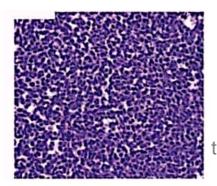
Active space
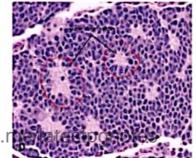
Neuroblastoma   00:08:08

- mc extracranial tumor of childhood

- Age – < 4 yrs

- mc site – Adrenal medulla

- N-myc gene amplification

- HPE – Small, round blue cell tumor of childhood
          (blue cells with scanty cytoplasm)

                    +

        Homer-wright pseudorosette

        (pseudo-cells present around the space filled with
        a material – Neuritic processes)

Small, round blue cells   cells present around a
                                      space filled with neuritic
                                      processes
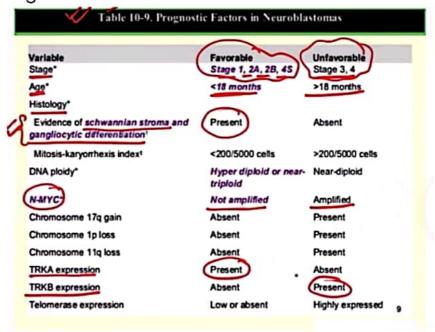
Small round blue cell tumors of childhood   00:12:01

1. Neuroblastoma
2. Retinoblastoma
3. medulloblastoma
4. Nephroblastoma
5. Hepatoblastoma
6. Ewing's sarcoma
7. PNET (primitive neuroectodermal tumor)
8. Rhabdomyosarcoma
9. Lymphoma

Active space

Prognostic factors in neuroblastoma

Variable	Favorable	Unfavorable
Stage*	Stage 1, 2A, 2B, 4S	Stage 3, 4
Age*	<18 months	>18 months
Histology*		
Evidence of *schwannian stroma and gangliocytic differentiation*¹	Present	Absent
Mitosis-karyorrhexis index¹	<200/5000 cells	>200/5000 cells
DNA ploidy*	*Hyper diploid or near-triploid*	Near-diploid
N-MYC*	*Not amplified*	Amplified
Chromosome 17q gain	Absent	Present
Chromosome 1p loss	Absent	Present
Chromosome 11q loss	Absent	Present
TRKA expression	Present	Absent
TRKB expression	Absent	Present
Telomerase expression	Low or absent	Highly expressed

Table 10-9. Prognostic Factors in Neuroblastomas

MEN – syndrome   00:14:55

- MEN – Multiple Endocrine Neoplasms

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Types

MEN – I   MEN – II a   MEN – II b/ III   MEN – IV

- Tumors associated with MEN Syndrome – Younger age
  - Synchronously/ metachronously occuring
  - more aggressive
  - multifocal

MEN I Syndrome

- A/K/A Wermer Syndrome

- It is due to defect in MEN I gene on 1/q chromosome

3 P's – Lesions of

Pituitary	Pancreas	Parathyroid
• Prolactinoma – mc	• occur in 30-70%	• occur in – 90%
• Occur in 30 – 40%	• Insulinoma m.c	• Parathyroid adenoma ↓ mc
	• Gastrinoma m.c Site – duodenum	

MEN 2A syndrome
00:18:48

- A/K/A Sipple Syndrome

- It is due to mutation in RET-gene on chromosome-10

a P's & 1 m

| Parathyroid tumors | Pheochromocytoma | medullary carcinoma of thyroid |

MEN 2B/3 Syndrome

- Due to mutation of RET-gene on chromosome 10

- Pheochromocytoma

- medullary carcinoma of thyroid

- 3 m's – marfanoid body habits
    - mucosal ganglioneuromas
    - medullary Corneal defects

MEN 4 Syndrome

- Due to mutation in CDKN1 gene on chromosome – 12

- Pituitary adenoma

- Parathyroid adenoma

- Reproductive gland tumor

- Renal / adrenal tumor

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Active space

DIABETES -I

WHO diagnostic criteria for diabetes mellitus   00:01:48

① Fasting plasma glucose ≥ 126 mg/dl
                    (FPG)

② Random plasma glucose ≥ 200 mg/dl

③ 2 hr plasma glucose ≥ 200 mg/dl by Oral Glucose Tolerance Test (OGTT)

④ HbA1c ≥ 6.5%

Pre Diabetes / Impaired Glucose Tolerance:
      WHO Diagnostic Criteria –

① Fasting Plasma Glucose 100–125 mg/dl

② Random Plasma Glucose 140–199 mg/dl

③ HbA1c 5.7–6.4%

- Diagnosis is made by performing these tests on seperate occasions ₹ days – Transient hyperglycemia can occur with acute states like infection, Burns, Trauma
(due to Catecholamine release)

Glycosylated Hemoglobin (HbA1c):

- Produced by non-enzymatic combination of glucose with → β globin chain – aka HbA1c

- Blood Glucose level over the life span of RBC i.e : 120 days

- Hence, one of the Best test for Diagnosis of DM

- Normal → HbA1c < 5.6%

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HbAlc

$< 5.6\%$ → Normal

$5.7-6.4\%$ → Prediabetic

$\geq 6.5\%$ → Diabetic

In a diabetic patient → maintain the HbAlc $< 7\%$

Classification of diabetes   00:14:19

1. **Type 1 diabetes** (β-cell destruction, usually leading to absolute insulin deficiency)
   Immune mediated
   Idiopathic
2. **Type 2 diabetes** (can range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance)
3. **Other specific types**
   Genetic defects of β-cell function
      Chromosome 20q, HNF-4α (MODY1)
      Chromosome 7p, glucokinase (MODY2)
      Chromosome 12q, HNF-1β (MODY3)
      Chromosome 13q, insulin promoter factor (MODY4)
      Chromosome 17q, HNF-1β (MODY5)
      Chromosome 2q, neurogenic differentiation 1/b-cell e-box transactivator 2 (MODY6)
      Mitochondrial DNA
      Others
   Genetic defects in insulin action
      Type 1 insulin resistance
      Leprechaunism
      Rabson-Mendenhall syndrome
      Lipoatrophic diabetes
      Others
   Diseases of the exocrine pancreas
      Pancreatitis
      Trauma/pancreatectomy
      Neoplasia
      Cystic fibrosis
      Hemochromatosis
      Fibrocalculous pancreatopathy
      Others
   Endocrinopathies
      Acromegaly
      Cushing's syndrome
      Glucagonoma
      Pheochromocytoma
      Hyperthyroidism
      Somatostatinoma
      Aldosteronoma
      Others

   Drug- or chemical-induced
      Vacor (pyriminil)
      Pentamidine
      Nicotinic acid
      Glucocorticoids
      Thyroid hormone
      Diazoxide
      β-Adrenergic agonists
      Thiazides
      Phenytoin
      Interferon alpha
      Others
   Infections
      Congenital rubella
      Cytomegalovirus
      Others
   Uncommon forms of immune-mediated diabetes
      "Stiff-man" syndrome
      Anti-insulin receptor antibodies
      Others
   Other genetic syndromes sometimes associated with diabetes
      Down's syndrome
      Klinefelter's syndrome
      Turner's syndrome
      Wolfram's syndrome
      Friedreich's ataxia
      Huntington's chorea
      Laurence-Moon-Biedel syndrome
      Myotonic dystrophy
      Porphyria
      Prader-Willi syndrome
      Others
4. **Gestational diabetes mellitus (GDM)**

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Type 1 diabetes mellitus   00:17:41

- 5-10% of patients

- Young adults

- due to Autoimmune β cell destruction → Insulin deficiency

Pathogenesis of Type I DM :

- 2 factors :   - Genetic factors

                - Environmental factors

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- Genetic factor :   -   HLA on short arm of Chr.6p

                        HLA DR3*, DR4*, DQ8*

                    -   Polymorphism in CTLA4, PTPN22

- Environmental – Virus : Coxsackie, Mumps
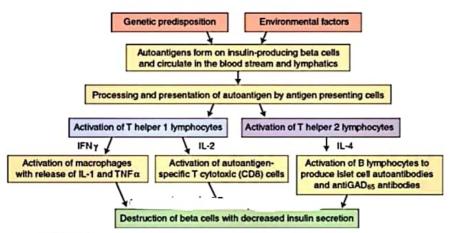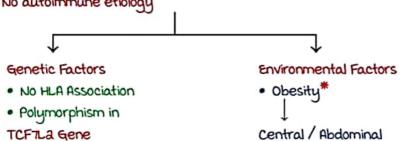
Figure 21-13 Pathophysiology of type 1 diabetes mellitus. *GAD*$_{65}$, glutamic acid decarboxylase; *INF-γ* Interferon-gamma; *IL*, interleukin; *TNF-α*, tumor necrosis factor-alpha

Type 2 Diabetes Mellitus   00:25:10

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- Insulin Resistance (+)

- No autoimmune etiology

Genetic Factors   Environmental Factors

• No HLA Association   • Obesity*

• Polymorphism in   Central / Abdominal

TCF7L2 Gene

- Cardinal features in pathogenesis of Type 2 DM :

   • ↓ Response of peripheral tissues – Skeletal muscle, Adipose

      tissue, liver to insulin = Insulin resistance

   • β cell dysfunction

Insulin Resistance :

- Failure of target tissue to respond normally to insulin
  - Failure to inhibit hepatic gluconeogenesis
  - Failure of glucose uptake ⌐
    Glycogen synthesis in skeletal muscle ⌐
  - Fat cells → failure to inhibit lipoprotein lipase
    ↓
    ↑ Circulation of free fatty acid

Obesity & insulin resistance   00:34:45

- Free fatty Acid (FFA) production :
  - Central adipose tissue is more lipolytic than peripheral → Excess
    FFA = Non esterified FFA (NEFFA)
  - Excess FFA → Accumulation of toxic intermediates
    Diacyl glycerol (DAG)
    ↓
    Attenuate Signaling through
    Insulin receptor pathway
    ↓
    Insulin resistance

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- Adipokines :

```
                        |
        ┌───────────────┴───────────────┐
        ↓                               ↓
Pre glycemic                    Anti glycemic
• Resistin                      • Leptin
• Retinol binding               • Adiponectin
  protein
```

- Inflammation : ↑ Cytokines
  ↓
  ↓ Insulin sensitivity

Active space

β cell dysfunction

00:41:00

• Insulin resistance → Impaired glucose tolerance.

• β Cell dysfunction → Development of Overt DM

    – Initially β cell function ↑

        ↓
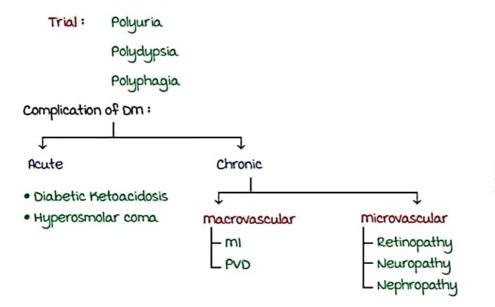
To Compensate for Insulin resistance

        ↓

Slowly – β cells exhaust their capacity

        ↓

        DM

Comparison	**Type 1**	**Type 2**
Clinical	onset <20 years	onset >30 years
	normal weight	obesity
	decreased blood insulin	normal or increased blood insulin
	anti-islet cell antibodies	no anti-islet cell antibodies
Genetics	ketoacidosis common	ketoacidosis rare
	human leukocyte antigen (HLA)-D linked	No HLA association
Pathogenesis	autoimmunity, immunopathologic mechanisms	insulin resistance
	severe insulin deficiency	relative insulin deficiency
Islet Cells	insulitis early	no insulitis
	marked atrophy and fibrosis	focal atrophy and amyloid deposits
	severe beta-cell depletion	mild beta-cell depletion

DM : Clinical features & complication

00:46:05

Trial :   Polyuria

          Polydypsia

          Polyphagia

Complication of DM :

```
                    Complication of DM
                    |
        ┌───────────┴───────────┐
        ↓                       ↓
      Acute                  Chronic
                        ┌───────┴───────┐
• Diabetic Ketoacidosis ↓               ↓
• Hyperosmolar coma  macrovascular   microvascular
                      ├ MI            ├ Retinopathy
                      └ PVD           ├ Neuropathy
                                      └ Nephropathy
```
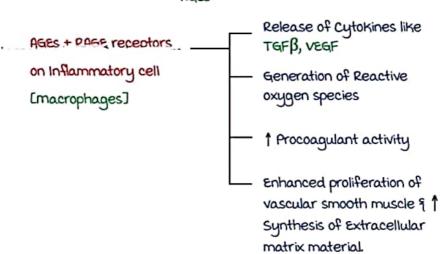
Pathogenesis of complications of DM   00:49:55

• Formation of Advanced Glycation End Products (AGEs)

– AGE's are produced by non enzymatic reaction between intracellular glucose intermediates like Glyoxal

+

Amino group of both Intra & Extra cellular protein

⇓

AGES

AGES + RAGE receptors on Inflammatory cell [macrophages]

— Release of Cytokines like TGFβ, VEGF

— Generation of Reactive oxygen species

— ↑ Procoagulant activity

— Enhanced proliferation of vascular smooth muscle & ↑ Synthesis of Extracellular matrix material.

Active space

DIABETES - 2

Pathogenesis of complication of diabetes mellitus $\quad$ 00:00:11
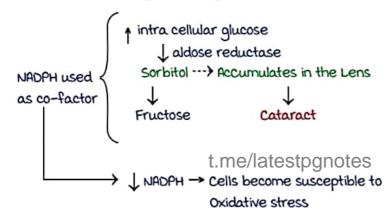
Formation of advanced end glycation products (m.c)
- Activation of protein Kinase - C:

$$\text{Intra cellular hyperglycemia}$$
$$\downarrow$$
$$\text{De-novo synthesis of Diacylglycerol (DGA)}$$
$$\downarrow$$
$$\uparrow \text{Production of VEGF, TGF - } \beta = \text{Chronic complication}$$

- Disturbance in Polyol pathway:

NADPH used as co-factor {
$\uparrow$ intra cellular glucose
$\downarrow$ aldose reductase
Sorbitol ---> Accumulates in the Lens
$\downarrow$ $\downarrow$
Fructose   Cataract
}

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$\longrightarrow$ $\downarrow$ NADPH $\rightarrow$ Cells become susceptible to Oxidative stress

Morphology of complications $\quad$ 00:05:20

- Pancreas

- $\downarrow$ in number & size of Islets $\rightarrow$ Type I DM
- Islet cell mass $\downarrow$
- Amyloid deposition (Type 2 DM)

- macro vascular:

- Atherosclerosis – endothelial injury
- myocardial Infarction – mcc of death in DM
- Hyaline Arteriosclerosis

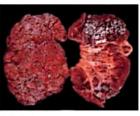Hyperplastic Arteriosclerosis $\rightarrow$ malignant Hypertension
$$\downarrow$$
Onion skin appearance

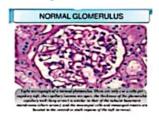**Hyaline deposition**

Active space

Diabetic nephropathy

00:11:28

- Renal failure → and mcc death in DM
- Gross pathology :
  • Diffuse granular appearance
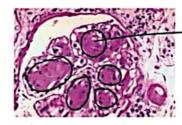
- • Glomerular changes–
  1) Capillary Basement membrane thickening
  2) Diffuse glomerulosclerosis
  3) Nodular glomerulosclerosis

NORMAL GLOMERULUS

Diffuse Glomerulosclerosis

Nodular Glomerulosclerosis

PAS+ NODULAR GLOMERULOSCLEROSIS
↓
KIMMELSTEIL WILSON LESION

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Thickened tubular basement membrane

- Nodular Lesion can be accompanied by prominent accumulation of hyaline material in capillary loops K/a Fibrin Caps
- if seen in Bowman's Capsule K/a Capsular drops
- Tubular changes:
  • Pyelonephritis
  • Necrotizing papillitis
- Vascular Changes: Arteriosclerosis
  Diabetic Retinopathy: → Proliferative
                        → Non proliferative

Other ocular lesions → Cataract, Glaucoma

Active space

SKIN

Blistering/bullous disorders of skin
00:00:26

Blistering disease

Subcorneal

- below stratum corneum

PEMPIGUS FOLIACESOUS

Suprabasal

- above stratum basale

PEMPIGUS VULGARIS

subepidermal

- below entire epidermis

BULLOUS PEMPHIGOID

A Subcorneal   B Suprabasal   C Subepidermal

Types of bullous disorders
00:03:14

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Pemphigus Vulgaris

- Shows Suprabasal bulla

Row of tombstone appearance

- Cause- IgG antibodies
- against desmogleins 1 & 3
- Immunofluorescence test

Shows Fish net appearance

Bullous pemphigoid

- Subepidermal bulla

- Cause – IgG antibodies against hemidesmosome Protein C
- Immunofluorescence test

Linear pattern

Dermatitis herpati formis

- Subepidermal bulla with neutrophils at the tip of dermal papilla

- Immunofluores-cence test

granular deposition

Active space

• Can be associated with gluten sensitive enteropathy
↓
Enteropathy associated T cell lymphoma.

Suprabasal bulla

Fish net appearance

Subepidermal bulla

Linear pattern

Subepidermal bulla with neutrophils

granular deposition.

Molluscum contagiosum   00:10:57

Cause
↓
Pox- virus

on Histopathological examination (H § E)
↓
• Molluscum bodies – Large (35 μ) homogenous, Cytoplasmic inclusions

• Usually seen in cells of Stratum granulosum § stratum corneum

Malignant melanoma   00:13:27
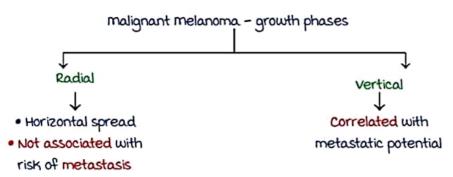
- **Highly aggressive tumor due to Sun exposure**
- **Two important Causative factors**
  - Genes
  - Sun exposure
- **mutations associated with malignant melanoma**
  - • Cell cycle regulators (P16/INK 4A)
  - • Growth factor receptors (KIT, RAS)
  - • Telomerase

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malignant melanoma - growth phases

- **Radial**
  - • Horizontal spread
  - • Not associated with risk of metastasis

- **Vertical**
  - Correlated with metastatic potential

- m.c type of malignant melanoma – Superficial Spreading
- on H & E – Deposition of melanin pigment
  Pleomorphic cells
- Immunohistochemical markers for Diagnosis
  ↓
  HMB – 45, melan A, S-100
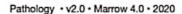
Epidermal tumors of skin - squamous cell carcinoma   00:18:02

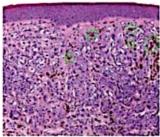- **2nd mc** Skin tumor

- **Risk factors**
  - Ionising radiation
  - UV rays
  - Actinic Keratosis
  - chronic ulcers
  - Arsenic

- **most important Cause**
  - DNA damage due to UV light

- **on H & E**
  - Keratin pearls
  - Desmosomes
  - Immunohisto chemical marker cytokeratin (CK)

Basal cell carcinoma (BCC)   00:21:23

- mc. invasive Carcinoma of Skin in humans (Locally invasive)
- Rarely metastasizes
- A/K/A rodent ulcer

- **mc mutation**
  - Sonic hedgehog Pathway
  - usually occurs at Sun exposed site in light coloured People

- **on H & E**
  - Cells resemble the basal layer of epidermis
  - cells in nodules, basaloid cells – with hyperchromatic nucleus

Active space

Basal cell carcinoma – cells
show two important
properties on slide
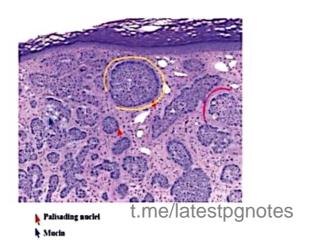
Peripheral palisading

↓

• Cells at the periphery of
nodules tend to be
arranged radially with
their long axis in parallel

Separation/Retraction
artefact

↓

• Space between
nodule and Stroma

↗ **Palisading nuclei**
↘ **Mucin**

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Few important terms in skin - pathology   00:26:22

1) Psoriasis – Munro's microabscesses
                 Spongiform pustules of Kogoj

2) Lichen planus – Band like lymphocytic infiltrate
                     Civatte/colloid bodies

3) Seborrheic Keratosis – appears as a part of paraneoplastic
                          syndrome (leser trelat sign).
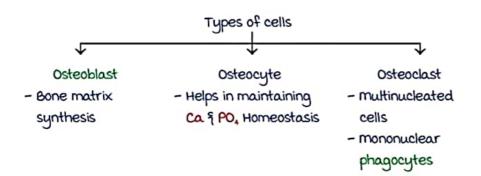
                              ↓

                    Seen in carcinoma of GIT

4) cylindroma – Jigsaw puzzle pattern on microscopy

5) Pilomatricoma – Ghost cells on microscopy.

Active space

BONE AND SOFT TISSUE

Bone - Introduction   00:00:07

Types of cells

Osteoblast	Osteocyte	Osteoclast
– Bone matrix synthesis	– Helps in maintaining Ca & PO_4 Homeostasis	– Multinucleated cells – mononuclear phagocytes

Bone disorders   00:02:00

a. Osteopetrosis
   - Also Known as
     • marble bone disease
     • Albers schonberg disease
   - Mutation in gene encoding carbonic anhydrase – 2 (CA-2)
   - Defect in osteoclastic activity

b. Paget's disease
   - ↑ in bone mass
   - mutation in SQSTm-I gene
   - Hallmark
        ⇓
     • mosaic pattern of lamellar bone
     • Jigsaw puzzle appearance
     • ↑ serum ALP (alkaline phosphatase)
     • mostly polyostotic

Note:
     • most common cancer of bone – Secondaries
     • most common 1° cancer of bone – Osteosarcoma

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Active space

Tumors of bone and cartilage

00:05:19

1. Osteosarcoma
   - most common site → metaphysis of long bones
   - metastasis via blood, mainly to lungs
   - most common mutation → Rb gene
   - microscopy
     - Osteoid/new bone formation
     - Eosinophilic and glassy in appearance

2. Chondrosarcoma
   - most common site → Pelvis, Ribs, Shoulder
   - Gross
     - Glistening white tumor
   - microscopy
     - Cartilaginous matrix
     - Lack of direct bone formation by tumor cells.

3. Osteoclastoma / Giant cell tumor
   - most common site → Epiphysis
   - Benign but locally aggressive
   - Neoplastic component → mononuclear cells, giant cells
   - Osteoclast like cells

4. Ewing's sarcoma/PNET
   - most common site → Diaphysis of long bones
   - most common mutation → t (11:22)
   - Gross
     - Periosteal reaction
   - X-ray
     - Onion skin appearance
   - microscopy
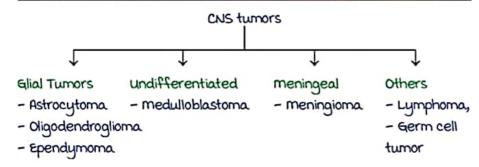   - Small, round blue cells with scanty cytoplasm
       +
       Homer wright rosettes

Active space

CNS TUMORS

- most common CNS tumors → Secondaries/metastasis
- most common secondary → small cell carcinoma of lung
- most common primary CNS tumor → Glioma > meningioma
- most common brain tumor in children → Pilocytic astrocytoma
- most common primary malignancy in children → Medulloblastoma

Classification of CNS tumors   00:02:35

```
                        CNS tumors
          ┌─────────────┬──────────────┬─────────────┐
          ↓             ↓              ↓             ↓
  Glial Tumors    Undifferentiated   meningeal      Others
  - Astrocytoma   - medulloblastoma  - meningioma   - Lymphoma,
  - Oligodendroglioma                               - Germ cell
  - Ependymoma                                        tumor
```

Anne mayo grading system:

```
     A              m              E              N
     ↓              ↓              ↓              ↓
  Atypia         mitosis      Endothelial     Necrosis
                              proliferation
```

I → None
II → Atypia
III → Atypia + mitosis
IV → AMEN

Astrocytomas   00:06:18

- WHO   I → Pilocytic astrocytoma
           II → Diffuse fibrillary astrocytoma
           III → Anaplastic astrocytoma
           IV → GBM: Glioblastoma multiforme

- Pilocytic astrocytoma:

    - mostly seen in children
    - mostly benign
    - most common primary, benign tumor in children.
    - usually seen in cerebellum, floor of 4th ventricle
    - grossly: cysts + mural nodules

★ Tumors showing mural nodules:
① Pilocytic astrocytoma
② Pleomorphic xantho astrocytoma

- microscopy: biphasic pattern → microcysts
  Rosenthal fibres
  Eosinophilic granular bodies (EGB)

Glioblastoma multiforme   00:11:35

- Usually seen in elderly
- Poor prognosis
- Frequently crosses the midline → Butterfly tumor
- microscopy : Nuclear pleomorphism
              high cellularity
              high mitosis

Endothelial vascular proliferation → Glomeruloid bodies
Serpentine geographical necrosis → pseudopalisading tumor cells

⇒   Glomeruloid bodies are also seen in yolk sac tumors and are
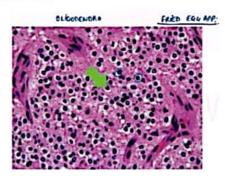   called Schiller Duval bodies

- WHO 2016 CNS tumor classification

IDH wild type	IDH mutant type
- Primary glioblastoma	- Secondary glioblastoma
- 90% cases	- 10% cases
- Supratentorial	- Infratentorial
- Age: 55y	- Age: 45y
- Mutations: TERT	- Mutations: p53
EGFR	
PTEN	
- Extensive necrosis	- mild necrosis
- Poor prognosis	- Better prognosis

Oligodendroglioma (WHO grade II)   00:19:02

- Age: middle – elderly
- usually affects cerebral cortex
- genetics: 90% cases are due to mutations of IDHI & IDH2 genes
  loss of Ip and 19q → highly chemosensitive

- microscopy:
  - cells with perinuclear halo: Fried egg appearance
  - calcifications
  - anastomosing vascular channels: Chicken wire blood vessels
  - movement of tumor cells around nerve fibres: perineuronal Satellitosis

- ★ Fried egg appearance is also seen in hairy cell leukemia
- ★ Calcifications are shown by following tumors:
    C → Craniopharyngioma
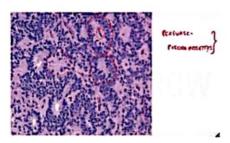   O → Oligodendroglioma
    m → meningioma.

Ependymoma   00:25:19

- Arises from ependymal lining
- Associated with NF- 2 gene mutations
- most common site in adults: spinal cord
- CSF dissemination is common.
- microscopy:
    Perivascular pseudorosettes : tumor cells surrounding
    a blood vessel
    → pseudorosette

Active space

Medulloblastoma

00:27:40

- Undifferentiated tumor → poor prognosis
- Most common primary malignant tumor in brain in children
- This tumor drops in the csf → drop metastasis
- Usually occurs in children
- Common sites: posterior fossa/cerebellum.
- microscopy:
  - sheets of small, round, blue cells with scanty cytoplasm
  - Homer wright rosettes

- Example of small round blue cell tumors of childhood :
  medulloblastoma
  Retinoblastoma → flexner wintersteiner rosettes
  Nephroblastoma
  Hepatoblastoma
  Neuroblastoma → Homer wright rosettes
  Ewing's sarcoma
  Primitive NeuroEctodermal Tumor (PNET)
  Rhabdomyosarcoma
  Lymphoma
- medulloblastoma is highly radiosensitive

Meningioma

00:33:57

- Benign tumor of adults
- Usually due to NF-2 gene mutations
- Progesterone responsive → ↑ incidence in pregnancy
- Previous radiation exposure is a risk factor.
- microscopy :- 5 Types
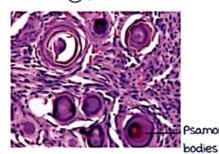 Transitional
  Spindle Cell
  Secretory
  Psammomatous
  Fibroblastic
  - Psammoma bodies : foci of dystrophic calcifications seen in:
    ① Papillary Ca of thyroid,
    ② Papillary renal cell carcinoma
    ③ meningioma

④ Serous cystadenocarcinoma of Ovary
⑤ Prolactinoma

Psamomma bodies

Types:

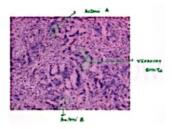| Atypical meningioma	Anaplastic, meningioma
clear cell choroid	Rhabdoid/papillary
– 4 or more mitosis/ HPF or at least 3 of the following * ↑ Cellularity * Prominent nucleoli * High nucleocytoplasmic ratio * Necrosis * Patternless growth	– > 20 mitosis/HPF

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Schwanomma   00:39:25

- Usually due to NF-2 gene mutations on chromosome 22 (merlin)
- Arises from inferior vestibulocochlear nerve (VIII CN)
- well circumscribed, encapsulated tumor
- microscopy: Antoni A → hypercellular area
  - Antoni B → hypocellular area
  - Verocay bodies → empty spaces in between the above 2

Neurofibroma   00:43:00

- Benign tumor
- mutations in NF-1 gene on chromosome 17 (neurofibromin)
- non- encapsulated tumor
* GFAP (glial fibrillary acidic proteins) positive brain tumors

Active space

Astrocytoma
Oligodendroglioma
Ependymoma
Medulloblastoma
Choroid plexus tumors

Warning : Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with Marrow Edition 4 videos.

Tuberous sclerosis and VHL   00:45:30

Tuberous sclerosis

- Autosomal dominant
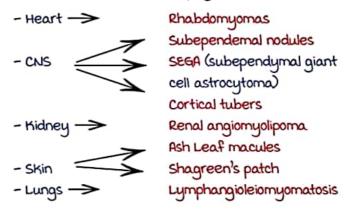- Caused by mutations in TSC I → Hamartin
                          TSC 2 → Tuberin

- Clinically:

TRIAD ⟨
- Seizures
- mental retardation
- Adenoma sebaceum
  (angiofibroma of nose)

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- Increased risk of developing other tumors:

- Heart → Rhabdomyomas
- CNS ⟨ Subependemal nodules
        SEGA (subependymal giant cell astrocytoma)
        Cortical tubers
- Kidney → Renal angiomyolipoma
           Ash Leaf macules
- Skin ⟨ Shagreen's patch
- Lungs → Lymphangioleiomyomatosis
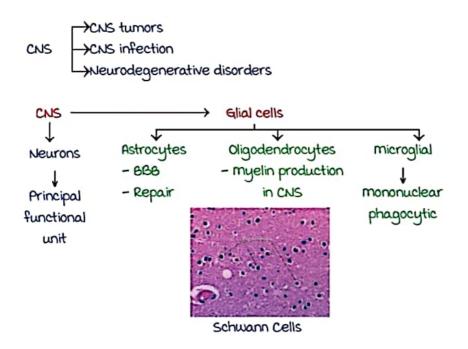
Von Hippel Lindau disease (VHL)

- Autosomal dominant
- Gene on chromosome 3p
- In Kidney   : clear cell renal cell carcinoma
  CNS   : Cerebellar hemangioblastoma
  Pancreas   : cysts
  Adrenals   : pheochromocytoma
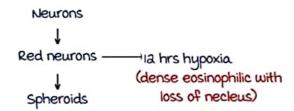 Skin   : epidermal cysts

Active space

NON NEOPLASTIC TUMORS OF CNS - 2

CNS ⟶ CNS tumors
⟶ CNS infection
⟶ Neurodegenerative disorders

CNS ⟶ Glial cells

Neurons | Astrocytes | Oligodendrocytes | microglial
↓ | – BBB | – myelin production | ↓
Principal | – Repair | in CNS | mononuclear
functional | | | phagocytic
unit

Schwann Cells

Response of injury in CNS   00:03:59

Characteristic feature – Cell loss

Neurons
↓
Red neurons ⟶ 12 hrs hypoxia
↓   (dense eosinophilic with
Spheroids   loss of necleus)

Gliosis – proliferation of glial cells.

→ Astrocytosis   – gemistoctyic astrocytes
                  – "Rosenthal fibres"
                      → Long standing gliosis
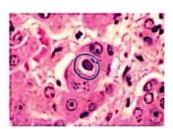   → Heat shock protein + ubiquitine

CNS infections

00:06:58

1. Rabies
   (enveloped RNA virus)
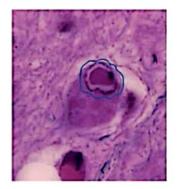
presence of "NEGRI BODIES"
   a) Intracytoplasmic
   b) Eosinophilic
   c) Composed of ribonucleo proteins
   d) Purkinje cells of cerebellum or pyramidal neurons of hippocampus

2. CMV infection
   a) Basophilic inclusion.
   b) Intractyoplamic or intranuclear inclusion.
   c) Clearing around inclusion.
   d) Owl eye inclusion

CNS infections

00:10:56

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3. HSV-I infection

   a) Cowdry inclusion.
   b) No clearing.
   c) Eosinophilic inclusion

4. Toxoplasmosis

   — Seen in HIV patients

Active space

HIV infection in CNS

- meningoencephalitis → MICROGLIAL nodules
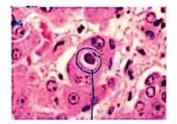- Toxoplasmosis
- Cmv infections ⎫ ↑ risk
- Primary CNS lymphomas ⎭

⎡ MICROGLIA
⎣ MULTINUCLEATED GIANT CELL
⎣ MONONUCLEAR CELL

5. Progressive multifocal leucoencephalpathy
   - Caused by JC polyomavirus
   - Immunocompromised
   - Affects oligodendroctyes
   - Demyelination
   - Ground glass appearance.

6. Prion diseases   15:47
   - Proteinaceous infections particle
   - No DNA, No RNA
   - Only proteins
   - AKA TSE (Transmissible spongiform Encephalpathy)

Diseases

Human

1. CJD* commonest
   (CREUTZFELDT-JAKOB DISEASE)
2. FFI (FATAL FAMILIAL INSOMNIA)
3. KURU (Cannibals)
   ↓
   Kuru plaques   PAS +
                   Congo red +

Animals

1. Scrapie (Sheep)
2. BSE (bovine spongiform encephalopathy)
3. mad cow disease

Pathogenesis of prion disease

α – helix   PrPc   Cellular prion protein
                ↓ mutation
β – pleated PrPsc   protease resistant
                ↓ acc. In brain
             APr   (Amyloid)

HPE: Spongiform swollen cells

Except FFI – Reactive gliosis & neuronal loss

Active space

Neurodegenerative diseases

00:21:22

Alzheimer's disease

- mcc of dementia in elderly
- Affects frontal, parietal and temporal lobes

Pathogenesis: Aβ amyloid

Genetic factors ⎯ Early onset ⎯ APP chr 21

PSI chr 14

PS2 chr 1

Late onset — Apo E₄ Chr. 19
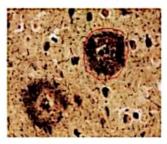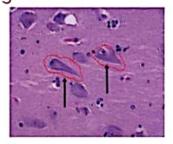
* Down's synd → ↑ APP ∵ 3 chromosomes no. 21

HPE

1. NEURITIC PLAQUES
   - Composed of Aβ 40 ₹ Aβ 42
   - Aβ core of neuritive processes exending

2. NEUROFIBRILLARY TANGLES
   - Composed of hyperphosphorylated tall proteins
   - Seen on SILVER stains

   Silver stain in CNS – Bielchowsky silver stain
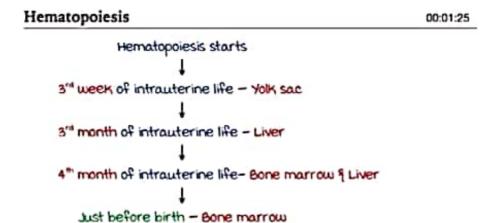
* Plaques ₹ tangles correlate with the degree of dementia

3. Hirano Bodies
   - Composed of active
   - Elongated bodies

4. Cerebral amyloid angiopathy

*Parkinson's d/s – Lewy bodies
* Amyotrophic lateral sclerosis – Bunina bodies (mutation in SOD-1)
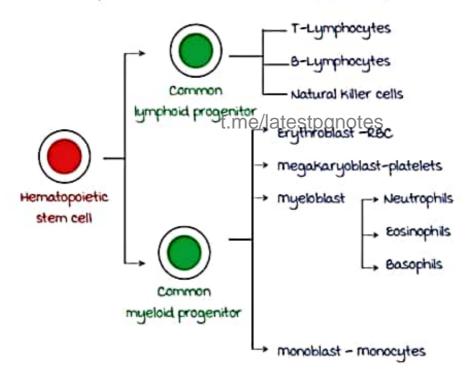
HEMATOLOGY- INTRODUCTION

Hematopoiesis   00:01:25

Hematopoiesis starts
↓
3ʳᵈ week of intrauterine life — Yolk sac
↓
3ʳᵈ month of intrauterine life – Liver
↓
4ᵗʰ month of intrauterine life– Bone marrow & Liver
↓
Just before birth – Bone marrow

- Hematopoiesis occurs in flat bones like ribs, sternum, pelvis

Common lymphoid progenitor
- T-Lymphocytes
- B-Lymphocytes
- Natural killer cells

Hematopoietic stem cell

Common myeloid progenitor
- Erythroblast –RBC
- megakaryoblast-platelets
- myeloblast → Neutrophils, Eosinophils, Basophils
- monoblast – monocytes

- The CD (clusters of differentiation) marker for hematopoietic stem cell-CD34

Active space
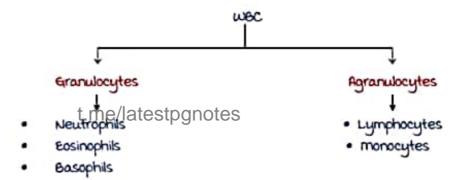
WBC –Disorders   00:07:58

- WBC (white blood cells) derived from
  myeloid series – myeloblast
  ↓
  Promyelocyte –Largest cell
  ↓
  myelocyte – deciding step to
  Eosinophil / basophil / neutrophil
  ↓
  metamyelocyte
  ↓
  Band Form
  ↓
  Neutrophil

  Progressive ↓ in cell size ←
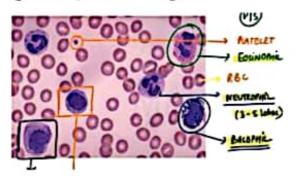
- Normal total leukocyte count – 4000–11000/mm³

WBC
- Granulocytes
  - Neutrophils
  - Eosinophils
  - Basophils
- Agranulocytes
  - Lymphocytes
  - monocytes

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Identification of WBC on peripheral smear   00:11:05

- Neutrophil – 3–5 lobes of nucleus with bluish granules in the cytoplasm
- Eosinophil – Binucleate /spectacle shaped nuclei with brick red granules in the cytoplasm
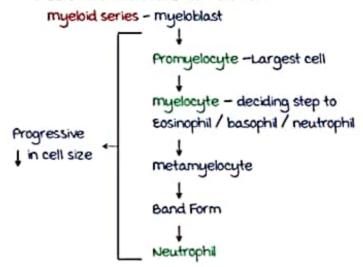- Basophil – Large bluish granules in cytoplasm which obscure the nucleus
- Lymphocyte – No granules in cytoplasm, no nucleoli
- monocyte – Largest cell, kidney shaped nucleus

(PIS)
→ PLATELET
→ EOSINOPHIL
→ RBC
→ NEUTROPHIL (3-5 lobes)
→ BASOPHIL

Non-neoplastic disorders of WBC'S   00:14:52

```
                    |
        ┌───────────────────────────────┐
        ↓                               ↓
   Leucopenia                      Leucocytosis
        ↓                               ↓
```

- ↓ WBC Count
- Usually due to neutropenia

- • ↑ WBC Count
- • Reactive proliferation of WBC

```
              Cause
        ┌──────────────┐
        ↓              ↓
  aplastic anemia   drug toxicity
```

- Agranulocytosis – clinically significant ↓ in WBCs mostly neutrophils
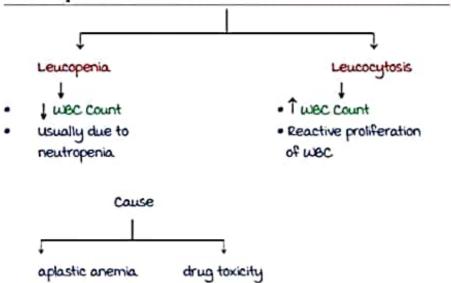
Neutrophilia
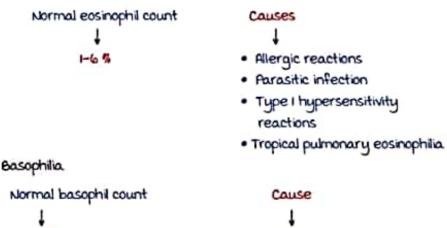
- ↑ neutrophil count
- Normal neutrophil count – 40–70%
- Causes – Acute infections
  - Tissue injury– like myocardial infarction, burns
  - Bacterial infections
  - myeloproliferate disorders like chronic myeloid leukemia (CML)

Eosinophilia/basophilia/lymphocytosis/monocytosis   00:19:35

Eosinophilia

```
Normal eosinophil count          Causes
        ↓                           ↓
      1–6 %
```

- • Allergic reactions
- • Parasitic infection
- • Type I hypersensitivity reactions
- • Tropical pulmonary eosinophilia

Basophilia

```
Normal basophil count            Cause
        ↓                           ↓
      < 1%                         CML
```

Lymphocytes

Normal lymphocyte count

15-40%

Causes
↓
- Tuberculosis –mc
- Viral infections
- Chronic infections
- Lympho proliferative disorders like Chronic Lymphocytic Leukemia (CLL); Acute Lymphoblastic leukemia (ALL)

monocytosis

Normal monocyte count
↓
2-8 %

Causes
↓
malaria
Endocarditis
Rickettsiosis
Viral infections

Morphological abnormalities of WBC's – in sepsis /anemia

00:25:29

peripheral smear in sepsis or infection

Toxic granules
↓
coarse & dark granules

Dohle bodies
↓
Patches of dilated endoplasmic reticulum

Neutrophil is present on PS

Hypersegmented
↓
- >5 lobes seen
- In megaloblastic anemia due to vitamin B12 deficiency

Hyposegmented
↓
- < 2 lobes seen
- In myelodysplastic syndrome
  ↓
  Pseudo pelger huet cell

Active space
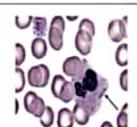
Morphological abnormalities – in May Hegglin anomaly/ chediak higashi syndrome

00:30:26

May Hegglin Anomaly:

- Giant Platelet – low platelet count
- Inclusion within the nucleus

Chediak Higashi syndrome

- Dark purplish granules in cytoplasm – Giant granules in neutrophils

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Alder Reilly abnormality

most of the neutrophils –have granules that obscure the nucleus

Neoplastic lesions of WBC

00:34:24

Leukemia
- involvement of bone marrow/peripheral blood
- leukemia can become lymphoma
- To identify → *flow cytometry* → IPT (immunophenotypic markers)

Lymphoma
- more systemic /tissue involvements → like lymph node/ spleen
- Lymphoma can become leukemia
- Histopathological diagnosis by markers

Leukemia

Acute
t.me/latestpgnotes
- ALL
- AML (Acute myeloid leukemia)

Chronic
- CLL
- CML

WBC Neoplasms

Lymphoid
- ALL
- Chronic lympho proliferative disorders

myeloid
- AML
- myeloproliferative disorders
- myelodysplastic syndrome
- MDS /MPN

Dendritic cells
- Langerhan's cell histiocytosis

Active space